Archives of Internal Medicine

VOLUME 58 AUGUST 1936 NUMBER 2

COPYRIGHT, 1936, BY AMERICAN MEDICAL ASSOCIATION

PITUITARY BASOPHILISM (CUSHING'S SYNDROME)

REPORT OF A VERIFIED CASE, WITH A DISCUSSION OF THE DIFFERENTIAL DIAGNOSIS AND TREATMENT

R. H. FREYBERG, M.D.

PAUL S. BARKER, M.D.

L. H. NEWBURGH, M.D.

AND

FREDERICK A. COLLER, M.D.

ANN ARBOR, MICH.

In 1932 Cushing [1] described the clinical syndrome of pituitary basophilism, now frequently referred to as Cushing's syndrome. In 1933 he published additional information pertinent to this interesting condition and listed fourteen verified cases reported in the literature. Most of these were originally recorded as examples of multiglandular disease. The significance of the pituitary lesion (if found at the time) was not appreciated.

The general interest in this newly described syndrome is indicated by the increasing number of cases recognized clinically. How many of these clinical diagnoses will be substantiated by pathologic proof time alone will tell. Eight cases [2] of the typical syndrome of pituitary basophilism in which a basophil adenoma of the pituitary gland was found at postmortem examination have been reported since Cushing's review (1933).[3] The important features of these cases, together with those of a verified case (herein reported), appear in table 1.

From the Departments of Internal Medicine and Surgery, Medical School, University of Michigan.

1. Cushing, H.: The Basophil Adenomas of the Pituitary Body and Their Clinical Manifestations (Pituitary Basophilism), Bull. Johns Hopkins Hosp. **50**: 137 (March) 1932.

2. Since these data were compiled, another verified case of pituitary basophilism presenting the clinical syndrome of Cushing's disease has been reported by J. H. Lawrence and H. M. Zimmerman (Pituitary Basophilism: Report of a Case, Arch. Int. Med. **55**:745 [May] 1935).

3. A case reported by Russell, Evans and Crooke (Lancet **2**:240 [Aug. 4] 1934) and another by Rutishauser (Deutsches Arch. f. klin. Med. **175**:640, 1933), in which pituitary basophilism was shown to exist at postmortem examination

(Footnote continued on next page)

TABLE 1.—*Verified Cases of Pituitary Basophilism Showing the Typical*

Case	Author	Year Reported	Sex	Age at Onset	Duration of Illness, Years	Clinical Observations								
						Obesity	Amenorrhea	Impotence (Sterility)	Hirsutism	Striae	Glycosuria	Basal Metabolic Rate	Blood Pressure	Skeletal Decalcification
1	Kepler [6a]; Kepler and others [6b]	1933	F	30	5	Neck, trunk, abdomen	+	..	+	+	+	−10 −12	160/120	Spine, skull, pelvis, femurs, compression fractures and gibbus
2	Marburg, O.: Arb. a. d. neurol. Inst. a. d. Wien. Univ. **35**: 143, 1933	1933	M	23	..	Face, abdomen	..	+	..	+	+	−28	Hypertension	Skull
3	Rutishauser, E.: Deutsches Arch. f. klin. Med. **175**: 640, 1933 (case 1)	1933	F	38	4½	Face, abdomen	+	..	+	..	..	−30 −27	Hypertension	.....
4	Rutishauser (case 3)	1933	F	..	Death at 65 years	Head, trunk	..	..	..	+ (?)	..	....	Hypertension	+
5	Craig, J., and Cran, B. S.: Quart. J. Med. **3**: 57 (Jan.) 1934	1934	F	24	4	Abdomen, thighs, upper part of arms	+	..	+	+	0	....	180/118	+
6	Russell, Evans and Crooke: Lancet **2**: 240 (Aug. 4) 1934	1934	M	29	2	Face, abdomen	..	+	..	+	..	....	210/140	.....
7	Wright, C. A.: M. Rec. **141**: 191 (Feb. 20) 1935	1935	M	10	1½	Face, neck, trunk	..	..	..	+	0	−18	154/110	Very thin vertebrae
8	Swan, W. G. A., and Stephenson, G. E.: Lancet **1**: 372 (Feb. 16) 1935	1935	F	26	4	Head, neck, trunk	+	..	+	+	..	....	160/100	.....
9	Freyberg and others.....	1935	M	12	7	Head, neck, trunk	..	+	..	+	0	− 3 −12 −24	175/155	+++

Postmortem Observations	Cause of Death	Comment
Basophil adenoma of pituitary gland 0.5 cm. in diameter; adrenal glands normal	.....	Autopsy performed elsewhere; pathologic study of pituitary gland only reported; at operation adrenal glands found to be normal
Basophil adenoma of pituitary gland 0.3 by 0.3 cm.; colloid goiter; adrenal glands larger than normal; arteriosclerosis present; slight glomerular capsular thickening	.....	No blood pressure reading; hypertension reported in fundoscopic examination
Basophil adenoma of pituitary gland 0.58 cm. in diameter, colloid goiter with adenoma; parathyroid glands fatty; pancreas normal; left adrenal gland very large, right 5.8 cm., combined weight 20 Gm., cortex broad, adenomatous, hyperplastic; gonads showed no follicles, few corpora lutea; arteriosclerosis present; osteoporosis ++	Apoplexy	Fat emboli in lungs
Pituitary gland showed diffuse predominance of basophils with numerous islands of basophils (serial sections); thyroid gland adenomatous; parathyroid glands very large, fatty; pancreas fatty; adrenal glands enlarged; gonads showed small, fibrotic corpora fibrosa; arteriosclerosis present; osteoporosis present with multiple fractures		
Basophil adenoma of pituitary gland 0.5 by 0.5 cm.; increased colloid of thyroid gland; parathyroid glands normal; thymus gland small, fatty; pancreas normal; adrenal glands enlarged, combined weight 35.7 Gm.; gonads normal; arteriosclerosis present	Purulent bronchitis and empyema	
Basophil adenoma of pituitary gland; thyroid gland distended with colloid; parathyroid glands normal; thymus gland small; pancreas normal; adrenal glands normal; active spermatogenesis; no osteoporosis; vascular degeneration in kidneys, "nephritis repens, type IV"	"Uremia"	Definite evidence of toxic type of chronic Bright's disease (nephritis repens IV) was cause of death in uremia
Large basophil adenoma of pituitary gland, with degeneration probably caused by roentgen rays; thyroid gland normal; parathyroid glands normal; adrenal glands entirely normal; gonads small; "grossly no decalcification of marked grade"	Death 4 days after appendectomy	Diabetic dextrose tolerance curve; blood cholesterol 176 mg. per hundred cubic centimeters
Basophil adenoma of pituitary gland; thyroid gland normal; fatty atrophy of parathyroid glands; thymus glands not found; fatty infiltration of pancreas; cortical hyperplasia of adrenal glands, especially of zona fasciculata; gonads normal; osteoporosis present		
Basophil adenoma of pituitary gland 0.4 cm. in diameter; thyroid gland showed abundant colloid; parathyroid glands not enlarged, fatty atrophy; thymus gland very large (85 Gm.), much lymphoid tissue; pancreas atrophic, numerous islands; adrenal glands showed marked hypoplasia, no adenoma; gonads small, complete aspermatogenesis; slight arteriosclerosis; osteoporosis +++; moderate subacute glomerulotubular nephritis and nephrosclerosis	Septicemia after exploration of left adrenal gland	Fat emboli found in lungs; marked fatty infiltration of liver

Several observations of unusual interest were made on our patient, and for that reason the case will be reported in detail.

REPORT OF CASE

History.—Z. K., a 19 year old youth of Polish descent, came to the University Hospital on Oct. 27, 1933, complaining of pain in the ankles when standing. At the age of 15 he fell from a moving wagon and suffered a contusion and laceration of the anterior middle third of the left leg. When he began to walk again (after a few days of rest in bed) he noted pain in the arches of the feet and in the ankles. Pain in the extremities became worse, and for four months prior to admission to the hospital it was necessary for him to use crutches to get about.

The patient enjoyed exceptionally good health as a child. No illness could be recalled. Growth and development had been normal until he was 12 years of age, when he began to gain weight rapidly. At the age of 15 he weighed 165 pounds (74 Kg.). His weight steadily increased, so that at the time of entering the hospital he weighed 185 pounds (82 Kg.). Growth in stature ceased at the age of 15, when he was 60 inches (152 cm.) tall. From puberty until two years before admission he had penile erections and seminal emissions; since then there had been impotence and lack of libido. For two years prior to admission epistaxes occurred about once a month, and slight polyuria and occasional nocturia had been noted. For a year he had noted palpitation and shortness of breath on slight activity, and for several months there had been edema of the ankles. His voice remained high pitched. He never shaved, although he occasionally clipped a soft beard with scissors.

Physical Examination.—The patient was 155 cm. tall and weighed 82 Kg. There was marked obesity, which was more noticeable on the face, neck and trunk. The face was round and florid. There were heavy jowls, large breasts and a protuberant abdomen. Over the shoulders, abdomen and lower extremities were numerous purplish striae. Hair was abundant on the scalp, axillae and pubis. A soft down covered his face. There was compound hyperopic astigmatism. The ocular fundi appeared normal. The visual fields were normal. The neck was short and thick. The voice was high pitched. The anteroposterior diameter of the chest was great. The pulmonary fields were clear. The heart was enlarged, the point of maximum impulse and the left border being 11.5 cm. to the left of the midsternal line. The blood pressure was 175 systolic and 155 diastolic. There was a thick abdominal panniculus. The penis and gonads were concealed in the pubic fat. The testes were small, about the size of almonds. There was a pigmented scar on the anterior aspect of the middle third of the left leg (site of previous trauma). Slight pitting edema of the ankles was present. The tendon reflexes were normal (figs. 1 and 2).

Laboratory Data on Admission.—The Kahn reaction of the blood was negative. Urinalysis gave negative results. The hemoglobin content was 90 per cent (Sahli). A blood count showed 5,000,000 erythrocytes per cubic millimeter and 11,800

have not been included in this group because the clinical syndrome characteristic of Cushing's disease was not present. Basophil adenomas of the adenohypophysis have been found in cases not showing clinical manifestations of basophilism. Thus, just as in other endocrine glands, notably the thyroid, an adenoma apparently may exist in the pituitary gland without causing any recognizable clinical abnormality. The incidence of adenoma in hypophyses removed during routine autopsies is being studied by one of us (R. H. F.) and will be reported in a separate communication.

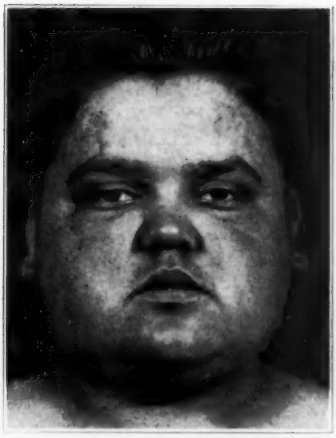

Fig. 1.—The appearance of the head and neck of the patient at the time he entered the hospital.

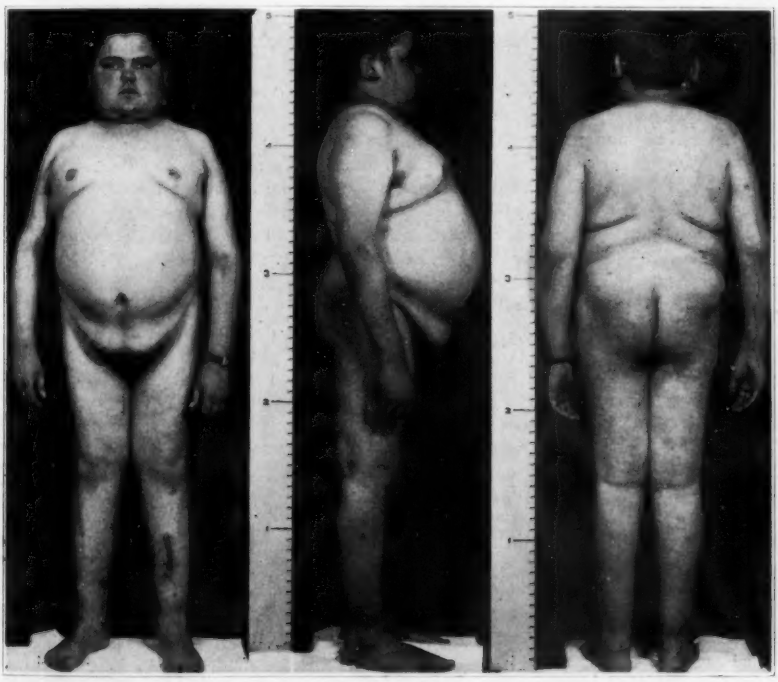

Fig. 2.—The appearance of the patient at the time of admission.

leukocytes. The differential leukocytic count was normal. Examination of the stool gave negative results. Chemical examination of the blood showed nonprotein nitrogen, 30 mg. per hundred cubic centimeters; cholesterol, 165 mg. (digitonin precipitation method of Windaus); calcium, 11.2 mg. (serum), and phosphorus, 2 mg. (serum).

A dextrose tolerance test (150 Gm. of dextrose ingested) gave the following results:

	Blood Sugar, Mg. per 100 Cc.	Urinary Sugar
Fasting	83	0
1 hour after ingestion of dextrose	192	0
2 hours after ingestion of dextrose	170	0
3 hours after ingestion of dextrose	107	0

Tests of renal function gave the following results: maximum specific gravity of the urine during a Lashmet-Newburgh concentration test, 1.028 (normal: 1.029 or above); urea clearance, 80 per cent of the mean normal; phenolsulfonphthalein excretion (6 mg. of dye, intravenously), 50 per cent in thirty minutes, 75 per cent in two hours. Analysis of the gastric contents showed: Fasting, no free hydrochloric acid; thirty minutes after the injection of 0.0005 Gm. of histamine hydrochloride, 22 degrees free hydrochloric acid, 30 degrees total acid; one hour, 36 degrees free hydrochloric acid, 46 degrees total acid; two hours, only a trace of free hydrochloric acid. The basal metabolic rate was —2 per cent. An electrocardiogram showed marked left axis deviation. The Ascheim-Zondek test, with a much larger amount of urine than usual, gave negative results. Mental tests revealed a mental age of 12 years and 1 month and an intelligence quotient of 81; the classification was dull normal intelligence.

Roentgen Examination (Dr. Carleton B. Pierce).—There were generalized demineralization of the entire skeleton and relative atrophy of all skeletal structures. The skull accentuated the relative diminution in the normal amount of calcium. The calvarium was very granular. The sella turcica was normal. The thorax was short and broad. The chondral ends of the ribs were somewhat frayed. There was a definite widening of the supracardiac soft tissue (suggesting persistent thymus). The pelvis demonstrated well the general decalcification; the bone shadow was no more dense than that of the filled urinary bladder (fig. 3). There was incomplete closure of the acetabular junction. The acetabular joint spaces were very irregular. The head of each femur was conical; that on the right was slightly fragmented. The neck of each femur was short and broad; the left showed some buckling. The cortex of the tibias and the fibulas were thin. The bones of the ankles and feet showed diminution of calcium content. The head of the first right metatarsal bone was flattened, and the head of each second metatarsal bone was fragmented. The elbows, forearms and wrists demonstrated delay in union of the epiphyses (fig. 4). The spine showed a most striking abnormality: There was marked rarefaction; the vertebral bodies had been reduced to an extremely thin meniscus, as a biconcave lens, and the intervertebral disks had swelled, so that they were almost spherical ("fish spine"); there was preservation of the epiphyseal centers of the anterior and posterior margin of the vertebral bodies (fig. 5). In summary, the roentgenograms demonstrated marked generalized skeletal decalcification without focal rarefaction and delay in closure of epiphyseal junctions (roentgen age, 15 years or less).

Course and Treatment.—A diagnosis of "Cushing's syndrome" with a basophil adenoma of the adenohypophysis was made (by P. S. B.). The calcium, phosphorus and energy exchange were studied for a period of five months. The results

of these studies are reported in separate papers.[4] During this time the patient was fed a reduction diet, supplying 890 calories. His weight decreased 22.5 Kg., so that he weighed 60 Kg. at the end of this period of study.[5]

The patient's condition improved. He became able to walk without the use of crutches and with less pain. As his weight was reduced, the blood pressure gradually fell, so that at the end of March 1934 it averaged 155 systolic and 125 diastolic. Frequent urinalyses during the entire study gave negative results. On March 27, 1934, the blood count showed: hemoglobin, 80 per cent (Sahli); erythrocytes, 5,300,000, and leukocytes, 12,250. Roentgenograms made on that date demonstrated no essential change in the skeleton.

Fig. 3.—Roentgenogram of the pelvis. The degree of decalcification is emphasized by the fact that the pelvic bones are no more opaque to the roentgen rays than the urine-filled bladder.

On March 29, 30 and 31 and April 2, 1934, the patient received roentgen therapy to the hypophysis as follows: 200 roentgen units (measured in air) was given through two portals 10 by 10 cm. (each temporal region) daily, with the central ray aimed at the pituitary fossa (total 1,600 roentgens). The factors were 200 kilovolt peak, 30 milliamperes, 50 cm. focal skin distance, a filter of 0.5 mm. of

4. Freyberg, R. H., and Grant, R. L.: Calcium and Phosphorus Metabolism in a Verified Case of Pituitary Basophilism, Arch. Int. Med., to be published. Freyberg, R. H., and Newburgh, L. H.: A Study of the Obesity and Energy Exchange in a Verified Case of Pituitary Basophilism, Arch. Int. Med., this issue, p. 213.

5. Footnote deleted by the authors.

copper plus 1 mm. of aluminum and 99 milliamperes per minute (each part 3.3 minutes as prescribed equals 200 roentgens).

The patient was discharged on April 5, 1934, advised to eat a 1,500 calory diet, rich in calcium and supplemented by 6 Gm. of calcium hydrogen phosphate ($CaHPO_4$) daily. When discharged, he weighed 60 Kg.

The patient returned on May 29, 1934, feeling about the same as at the time of discharge. He had been up and about the house and doing light work about a farm. The findings on physical examination were essentially the same as when he was discharged. The weight was 66.5 Kg. (He had not been able to stay on

Fig. 4.—Roentgenogram of one wrist, showing the ununited epiphyses.

his diet). The blood pressure was 160 systolic and 130 diastolic. There was slight edema of the ankles.

Laboratory data at that time were as follows: The urine was normal. The hemoglobin content was 75 per cent (Sahli); the erythrocytes numbered 4,050,000 per cubic millimeter, and the leukocytes, 9,800. The stool was normal. Tests of renal function gave the following results: Maximum specific gravity of the urine during the Lashmet-Newburgh concentration test, 1.028; urea clearance, 104 per cent of the mean normal; phenolsulfonphthalein excretion (6 mg. of dye intravenously), 26 per cent in fifteen minutes, 68 per cent in two hours. The plasma contained 6.96 Gm. of protein per hundred cubic centimeters—albumin, 4.76 Gm., and globulin, 2.2 Gm. The albumin-globulin ratio was 2.16. Roentgen examina-

tion revealed further destruction of the head of the left femur; otherwise there was no skeletal change.

Calcium and phosphorus studies were carried out over another period of three months, throughout which time the clinical status remained essentially unchanged except for reduction in weight in response to undernutrition (900 calory diet). On Aug. 22, 1934, he was again discharged. At that time he weighed 58 Kg.

The patient returned during the latter part of September 1934. There was no appreciable change in the symptoms or in the results of laboratory tests. The

Fig. 5.—A lateral roentgenogram of the spine, showing the marked decalcification and the thin biconcave vertebral bodies separated by large intervertebral disks (fish spine).

weight was 59.3 Kg. The blood pressure was 175 systolic and 135 diastolic. During the time this patient was studied, several members of the Mayo Clinic [6]

6. (*a*) Kepler, E. J.: Polyglandular Dyscrasias Involving Abnormalities of Sexual Characteristics: Report of Four Cases, Proc. Staff Meet., Mayo Clin. **8:** 102 (Feb. 15) 1933. (*b*) Kepler, E. J.; Kennedy, R. L. J.; Davis, A. C.; Walters, W., and Wilder, R. M.: Suprarenocortical Syndrome and Pituitary Basophilism: Presentation of Three New Cases, Proc. Staff Meet., Mayo Clin. **9:**169 (March 21) 1934. (*c*) Walters, W.; Wilder, R. M., and Kepler, E. J.: The Suprarenal Cortical Syndrome: Report of Two Cases with Successful Surgical Treatment, Proc. Staff Meet., Mayo Clin. **9:**400 (July 3) 1934.

reported cases of a syndrome similar to that of our patient, in which a cortical adrenal tumor or hyperplasia was found, with cure after the removal of the tumor or of part of the hyperplastic glands. Because roentgen therapy to the pituitary body was followed by no improvement in our patient, it was decided to explore the adrenal glands surgically. Intravenous pyelographs showed no evidence of displacement or distortion of either kidney. On Oct. 1, 1934, the left adrenal gland was explored (by F. A. C.). The gland contained no tumor but was thought to be considerably longer than normal. The lateral half was removed. It was felt wise to delay exploration of the right adrenal gland until a later date.

Microscopic examination of the portion of left adrenal gland by Dr. C. V. Weller revealed: "A portion of thin, flat adrenal gland, showing hypoplasia of

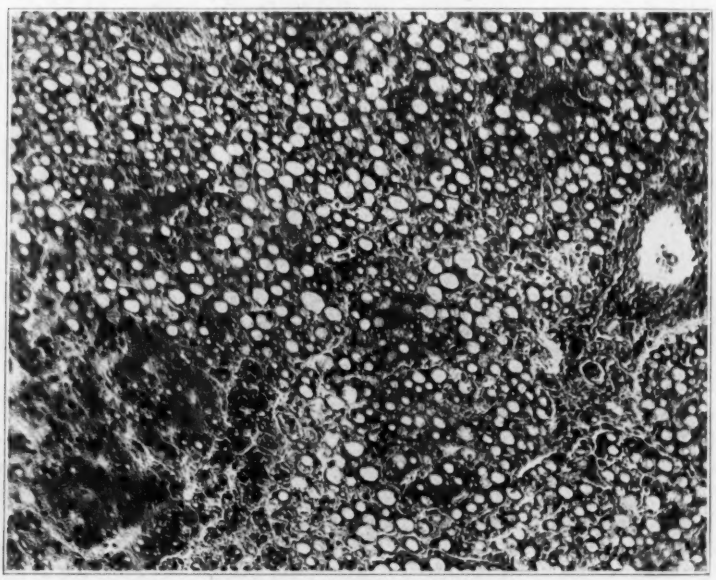

Fig. 6.—A section of the liver, showing the marked infiltration of fat.

the cortex and a reduced medulla. The cortex shows well marked lipoidosis, and there is a small mononuclear infiltration in the cortex. The cortical cells are distinctly smaller than normal. It is not safe to judge functional activity on this ground, however, since the small size of the cells might indicate low output, or, conversely, the cells may be small because of increased rate of output."

Pneumonia developed, and a severe infection with Streptococcus haemolyticus spread from the wound through almost the entire abdominal subcutaneous tissue. Septicemia (Str. haemolyticus) developed. The patient died on Oct. 11, 1934.

Autopsy (Dr. C. V. Weller).—Besides those concerning the endocrine system, which will be described in detail, the following observations are of interest: The lungs showed extensive fatty embolism. In the liver there was marked fatty infiltration, involving practically the entire lobule (fig. 6). There were several small adenomas of the bile ducts. The gallbladder contained three pigmented cholesterol

calculi. The kidneys showed cloudy swelling, deposits of lime salt in the tubules and multiple acute and chronic inflammatory foci, with infiltration by lymphocytes and plasma cells. Glomerulotubular nephritis was present in moderate degree (fig. 7). Occasional arterioles showed sclerosis (fig. 8).

The abdominal aorta contained patches of intimal lipoidosis and atheromatous plaques. All bones examined showed marked osteoporosis. The vertebrae could be easily cut with a knife. Microscopic examination revealed marked osteoporosis, with fatty marrow. In areas of growth there was a retardation of the transformation of cartilage into bone, with areas of rather cellular cartilage left among the trabeculae of the bone.

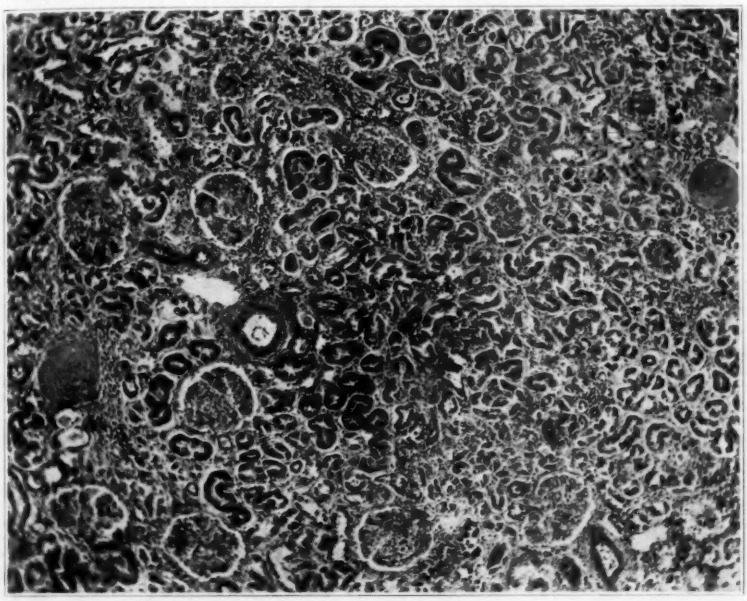

Fig. 7.—A section of kidney showing scarred glomeruli and areas of cellular infiltration.

The Endocrine System.—The hypophysis was slightly larger than normal. Cut sections showed an atypical grayish-pink cellular area in the anterior lobe, extending into the pars intermedia (fig. 9).

Microscopic examination revealed marked congestion. Eosinophils were in slight excess in the anterior lobe. There was moderate edema of the pars nervosa. The atypical cellular area seen in the gross specimen was composed of cells larger than any of the normal cells of the anterior lobe. With Mayer's hemalum (1 Gm. hematoxylin, 50 Gm. potassium alum, 0.2 Gm. sodium iodate and 100 cc. distilled water) and eosin the cytoplasm stained purplish blue, whereas eosinophils (in the surrounding portion of the gland) were clearly demonstrated in the same preparation. With special stains, granules were imperfectly demonstrated that tended

toward basophilic. This appeared to be an adenoma of imperfect differentiation, slightly basophilic (figs. 10 and 11).

(A portion of the material was sent to Dr. Harvey Cushing and Dr. Eisenhardt, who gave the following opinion regarding the adenoma): "We think

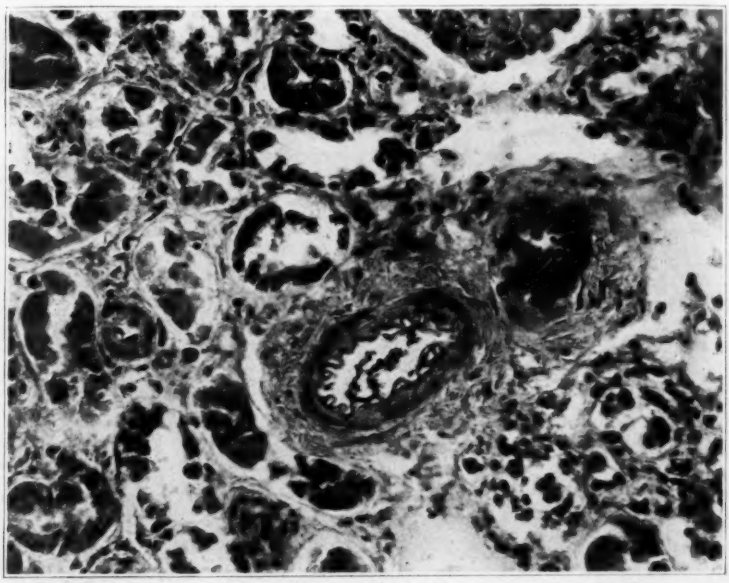

Fig. 8.—A section of kidney under greater magnification, showing arteriolar fibrosis.

Fig. 9.—The pituitary gland sectioned longitudinally.

that the lesion in the pituitary sections you have sent us is a typical basophilic adenoma."

Dr. Percival Bailey also examined sections of this gland and allowed us to quote him as saying: "It is quite impossible to determine accurately the nature of this tumor because of improper fixation and inadequacy of the material sub-

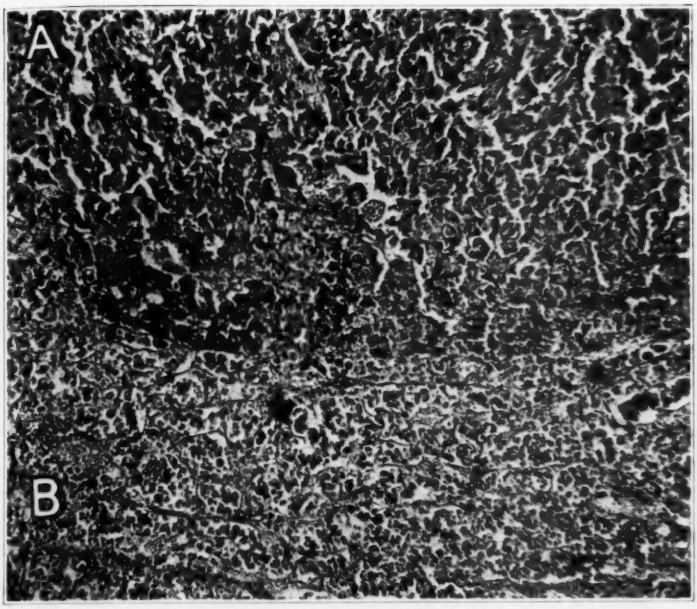

Fig. 10.—A section across the adenohypophysis, showing (*A*) the adenoma and (*B*) the surrounding adenohypophysis.

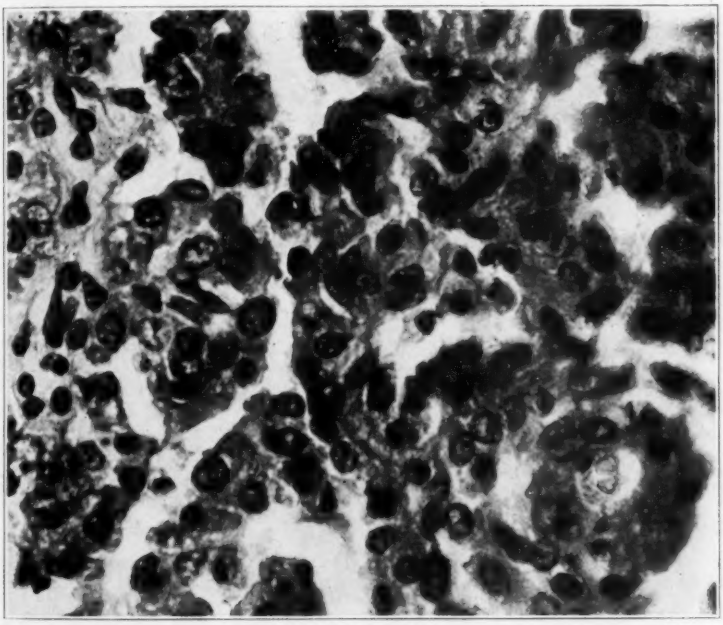

Fig. 11.—The appearance of the hypophyseal adenoma under greater magnification.

mitted. However, it is my opinion that the tumor contains a large number of basophilic cells. There are no eosinophilic cells. It is impossible to determine with any degree of certainty the nature of the majority of the cells composing the tumor."

The right adrenal gland measured 5 by 4 by 8 cm. The cortex and medulla were thin; there was no neoplasm.

Microscopic examination revealed marked hypoplasia (fig. 12), congestion and infiltration by lymphocytes and plasma cells, particularly in the medulla. There were agonal bacterial emboli.

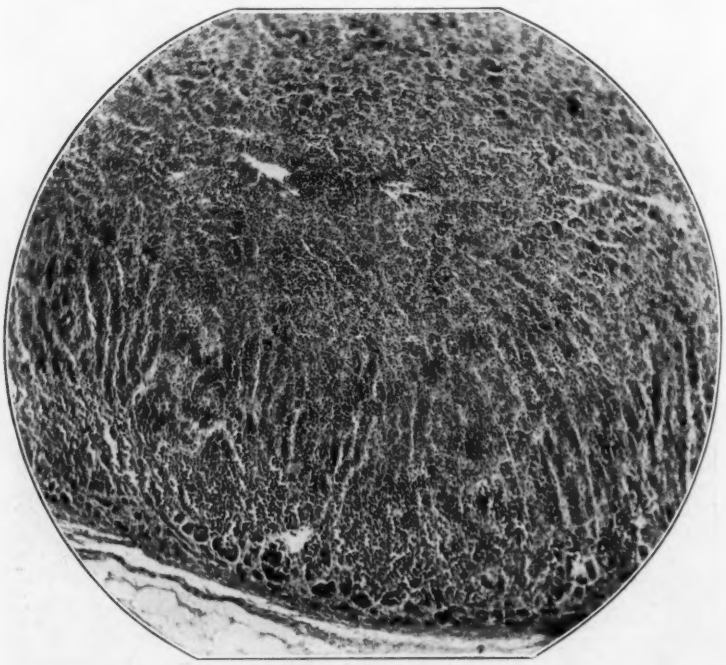

Fig. 12.—A cross-section of the right adrenal gland under low power magnification, showing the atrophic cortex and the scanty medulla.

The remainder of the left adrenal gland was similar to the right and, in addition, showed surgical hemorrhage and areas of necrosis.

The thymus measured 9 by 6 by 1.5 cm. and weighed 85 Gm. (very large for the age of the patient). It was made up of a considerable amount of pinkish-gray lymphoid tissue but little fat, was somewhat nodular and contained no evidence of neoplasm (fig. 13).

Microscopic examination revealed very marked lymphoid hyperplasia (fig. 14).

The thyroid gland was not enlarged. Colloid was fairly abundant. There was no adenoma.

Fig. 13.—The thymus as it lay in the thorax. Practically no fat was found in this large fleshy gland.

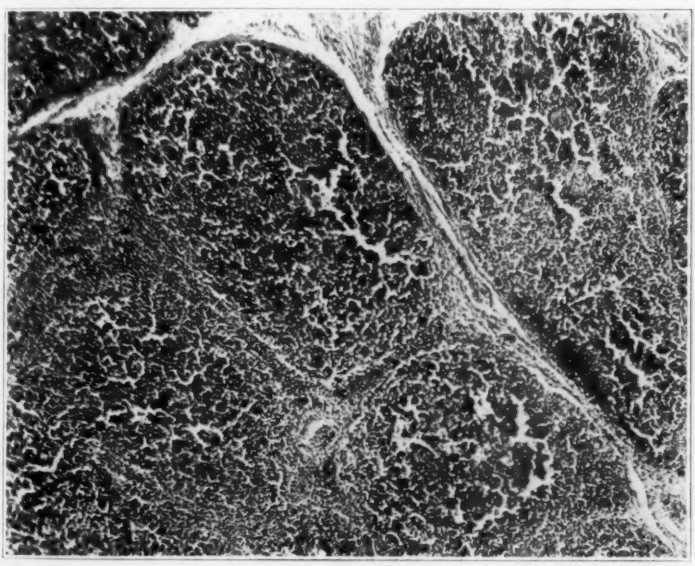

Fig. 14.—A section of the persistent hyperplastic thymus under low power magnification. Note the lobular architecture and the numerous "thymic corpuscles."

Microscopic examination revealed colloid in normal amount, no adenoma and no evidence of Graves' constitution. Staining for fat showed no lipoidosis of the epithelium.

The parathyroid bodies were not enlarged. The largest of the four dissected was the size of a small pea. Microscopic examination showed: advanced fatty atrophy, more than half of the glandular epithelium being replaced by adipose tissue; no adenoma was present (fig. 15).

The pancreas was of average size. Microscopic examination revealed fatty atrophy and also simple atrophy of the acini. The islands were numerous and averaged larger than normal (fig. 16).

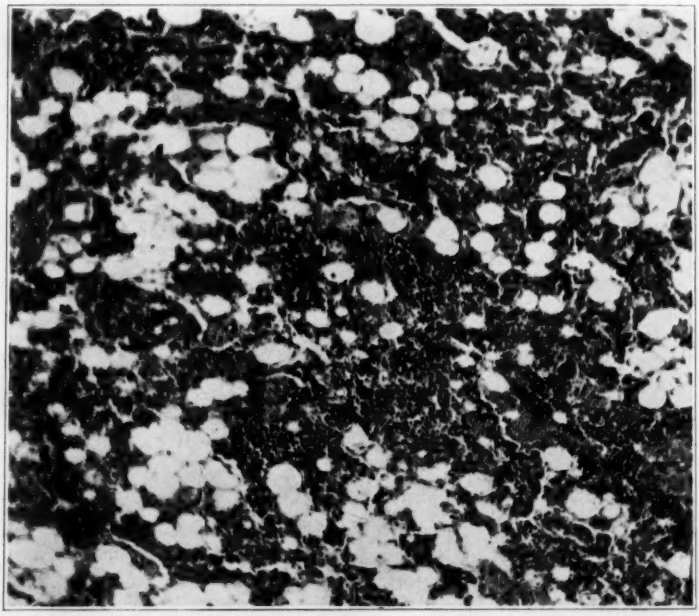

Fig. 15.—A section through a parathyroid gland showing the marked fatty infiltration.

The testes were small, about the size of an almond. Microscopic examination showed them to be in a preadolescent stage of development, with complete aspermatogenesis (fig. 17).

Pathologic Diagnosis.—The diagnosis was: septicemia; infected surgical wound, with diffuse phlegmon of the panniculus and muscle and erysipelatous inflammation of the lower abdominal wall; agonal bacterial embolism in both adrenal glands; massive pulmonary fat embolism, with pulmonary hemorrhage, emphysema and atelectasis; polyglandular dyscrasia (Cushing's syndrome of pituitary basophilism) basophil (?) adenoma of the pituitary body, marked hyperplasia of the thymus gland, hypoplasia of the adrenal glands and aorta, hyperplasia and hypertrophy of the islands of Langerhans, fatty atrophy of the parathyroid glands,

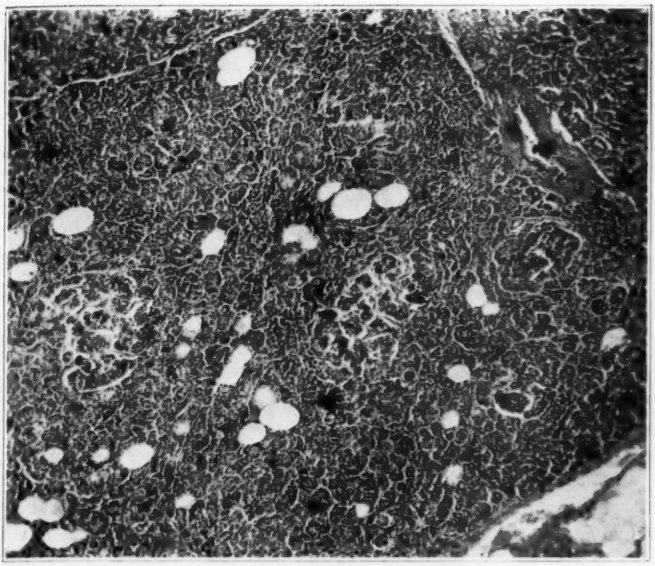

Fig. 16.—A section of the pancreas, showing the numerous large islands of Langerhans.

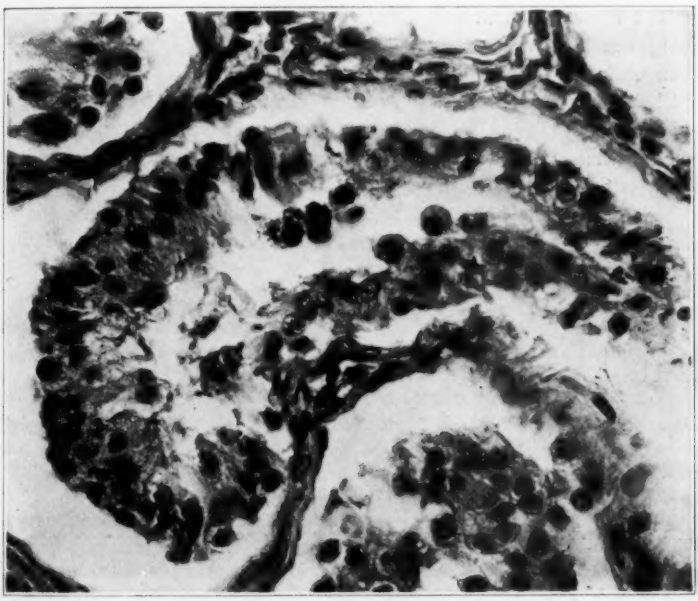

Fig. 17.—A single seminiferous tubule showing aspermatogenesis. A few aborted attempts at sperm formation are shown in the lumen.

hypoplasia of the genitals, aspermatogenesis, lipoidosis of the liver, obesity and generalized osteoporosis; subacute glomerulotubular nephritis, cholelithiasis, moderate hypertrophy of the left ventricle, tuberculosis of the bronchial nodes, acute passive congestion and parenchymatous degeneration of all organs.

Chemical analyses of bone obtained at autopsy were made.[7] The ash of the femur was found to be 53 per cent; that of the rib, 50 per cent. These values are considerably lower than normal. The brain tissue (cerebrum and cerebellum) contained 8.6 mg. of calcium per hundred grams of tissue. The sterol content of portions of cerebrum and cerebellum was 2.34 Gm. per hundred grams of tissue.

COMMENT

There is no doubt that this patient exhibited the features which correspond in detail to those that Cushing described and attributed to basophil adenoma of the hypophysis. Most of the reported cases occurred in women. Only two of the fourteen verified cases reported by Cushing[8] were in men. Of the nine additional verified cases listed in table 1, four were in men. Hirsutism, so uniformly a feature of the syndrome in women is not encountered in men. The absence of this feature and of amenorrhea adds to the difficulty of recognition of the syndrome in men.

Our patient at no time demonstrated glycosuria. Although common, this abnormality is by no means a constant finding in pituitary basophilism. The dextrose tolerance test showed a delay in oxidation of dextrose similar to that seen in persons with diabetes.

The basal metabolic rate seems to have no characteristic deviation from normal in the reported cases. Most commonly it is low, although it ranges from — 40 to + 42 per cent.

Skeletal decalcification has been noted in the majority of cases. It has often been slight. The extreme generalized demineralization of the skeleton, the "fish spine" and the persistent epiphyseal lines exhibited by our patient are especially striking features.

Several of the observations at autopsy on our patient are of unusual interest. In the majority of the reported cases the thymus gland was atrophic; in some it was almost completely replaced by fat; in a few it was normal in size. The thymus gland in a case reported by Teel[9] weighed 24 Gm. and was said to be hyperplastic. In our patient, the thymus was huge. It weighed 85 Gm. and consisted almost entirely of

7. For the determination of bone ash, small sections of a femur and a rib were dried, extracted with alcohol and ether, again dried and then ashed at a dull red heat in a muffle furnace. Total ash was calculated on the moisture-free, fat-free basis.

8. Cushing, H.: "Dyspituitarism": Twenty Years Later, with Special Considerations of the Pituitary Adenomas, Harvey Lectures, 1932-1933, Baltimore, Williams & Wilkins Company, 1934, p. 90.

9. Teel, H. M.: Basophilic Adenoma of the Hypophysis with Associated Pluriglandular Syndrome: Report of a Case, Arch. Neurol. & Psychiat. **26**:593 (Sept.) 1931.

lymphoid tissue. The rôle played by the thymus gland in these cases is apparently not important, since the characteristic features of the syndrome exist no matter what the state of this organ. It may very well be, however, that the stormy course which followed operation in our patient was in part resultant from this persistent hyperplastic thymus gland.

In most of the verified cases of pituitary basophilism, the adrenal bodies were hyperplastic; some contained adenomas. In our case, these glands, although long, were very thin and contained a distinctly hypoplastic cortex (most marked in the glomerular zone). The medulla was also scanty.

Cushing [8] suggested that the hypertension associated with this syndrome might be explained on the basis of basophilic activation of the neurohypophysis and that it need not be ascribed to an adrenal source. It should be noted that in three of Cushing's group of verified cases and in four of those listed in table 1 (numbers 1, 2, 7 and 8) the adrenal bodies were reported to be normal. This lack of recognizable adrenal abnormality in some cases and the occurrence in our patient of adrenal glands with hypoplastic cortices, without adenomas and with scanty medullary tissue, certainly support the contention that the hypertension in these cases is not necessarily due to adrenal changes but may be directly the result of the pituitary lesion.

MacMahon, Close and Haas [10] studied the cardiovascular renal changes in two cases of basophil adenoma of the anterior lobe of the pituitary and found that the kidneys showed pathologic changes characteristic of "malignant nephrosclerosis." In our patient the renal damage was not sufficient to cause abnormalities of the urine or any appreciable impairment of renal function. Microscopic examination of the kidneys showed a mixture of inflammatory and degenerative changes, and occasional arterioles were sclerosed.

DIFFERENTIAL DIAGNOSIS

The clinical diagnosis of pituitary basophilism depends on recognition of the syndrome so completely described by Cushing. However, cases have been reported in which all the clinical characteristics of "Cushing's syndrome" of pituitary basophilism were present but in which the hypophysis was found to be entirely normal when sectioned serially. In these cases lesions were found elsewhere, most commonly in the adrenal glands. Frank [11] recently mentioned two cases diagnosed

10. MacMahon, H. E.; Close, H. G., and Haas, G.: Cardiovascular Renal Changes Associated with Basophil Adenoma of the Anterior Lobe of the Pituitary (Cushing's Syndrome), Am. J. Path. **10**:177 (March) 1934.

11. Frank, R. T.: A Suggested Test for Functional Cortical Adrenal Tumor, Proc. Soc. Exper. Biol. & Med. **31**:1204 (June) 1934.

TABLE 2.—*Cases of Cortical Adrenal Lesion or Neoplasm of the Thymus*

Case	Author	Year Reported	Sex	Age at Onset	Duration of Illness	Clinical Diagnosis	Clinical Findings: Obesity	Amenorrhea	Impotence or Sterility	Hirsutism	Cutaneous Striae	Glycosuria	Basal Metabolic Rate	Blood Pressure	Skeletal Decalcification
1	Hunter, C.; McMillan, J. C.; Boyd, W., and Cameron, A. T.: Canad. M. A. J. **25**: 188 (Aug.) 1931	1931	F	28	2 yrs.	Tumor of adrenal cortex with metastases	+	+	..	+	+	+	....	156/120	Lumbodorsal spine
2	Weith-Pederson, G.: Hospitalstid. **74**: 1231 (Dec. 24) 1931	1931	F	..	.....	Malignant adrenal tumor with metastases	+	..	..	..	+	..	....	245/150	.....
3	Kepler [6a]	1933	F	30	2 mos.	"Polyglandular dyscrasia"	0	?	..	+	..	+	+ 4	Normal	Slight in ribs, pelvis and femur
4	Kepler and others [6b]	1934	F	31	1 yr.	Adrenal cortical syndrome	Trunk and face	+	..	+	+	0	−15	168/118	Spine
5	Kepler and others [6b]	1934	F	24	1 yr.	Adrenal cortical syndrome	Face, neck and trunk	+	..	+	+	+	+ 1	180/120	Slight, of spine
6	Kepler and others [6b]	1934	F	4	5 yrs.	Adrenal cortical syndrome	Face, neck and trunk	Precocious menses	..	+	+	..	−20	132/ 97	Bones of child aged 12 years
7	Walters and others [6c]	1934	F	38	5 mos.	Adrenal cortical syndrome	Face	+	..	+	..	0	Normal	170/102	Slight, of spine
8	Walters and others [6c]	1934	F	31	5 mos. 10 mos. 12 mos. 14 mos.	? ? ? Adrenal cortical syndrome	Face Decreased Increased Increased	0 + ...	.. ..	Slight ? .. 0	 0	+ 0* .. +	....	150/100 116/ 76 ..... 158/ 96	.....
9	Kepler [6a]	1933	F	45	4 mos.	Tumor of adrenal cortex suspected	Face and neck	+	..	+	..	+	+20	176/ 80	Slight, in spine; compression sixth thoracic vertebra
10	Lescher, F. G., and Robb-Smith, A. H. T.: Proc. Roy. Soc. Med. **27**: 404 (Feb.) 1934	1934	F	32	4 yrs.	Carcinoma of cortex of left adrenal gland	Face, neck and trunk	..	..	+	+	+	....	205/155	General decalcification and multiple fractures
11	Wright, C. A.: M. Rec. **141**: 191 (Feb. 20) 1935 (case 4)	1935	F	22	18 mos.	Carcinoma of adrenal cortex	Face, neck and trunk	..	..	+	+	..	+ 4	156/120	Spine
12	Leyton, O.; Turnbull, H. M., and Bratton, A. B.: J. Path. & Bact. **34**: 635 (Sept.) 1931	1931	M	30	1 yr.	No diagnosis made	Face and abdomen	..	+	..	+	+	....	170/100	None
13	Leyton, O.: Lancet **1**: 1221 (June 9) 1934	1934	M	11	3 mos.	Disease of pituitary gland or of adrenal glands	Face and abdomen	..	+	..	0	+	....	125/ 85	.....
14	Brown, W. H.: Lancet **2**: 1022 (Nov. 17) 1928	1928	F	45	.....	Plurigland-ular defect	Generalized	..	..	..	..	+	+20	240/160	.....

Gland Showing Many or All of the Characteristics of Pituitary Basophilism

Pathologic Condition	Comment
Tumor of right adrenal gland larger than a fetal head.....	No autopsy; diagnosis of tumor of adrenal cortex made from pathologic examination of vaginal metastases
Pituitary gland said to be normal; not examined microscopically; malignant neoplasm of adrenal gland 12 by 6 cm.	
Thyroid gland not examined; thymus gland not examined; carcinoma of entire head of pancreas; metastases in liver; carcinoma of left adrenal gland (operation)	Physical characteristics not typical of Cushing's syndrome; reaction to Friedman test positive
Pituitary gland normal (serially sectioned); thyroid gland atrophic, fatty; combined weight of adrenal glands 35 Gm.; both enlarged; normal histologic picture except for two small adenomas in left cortex; gonads small, sclerotic, with small cysts	
Adenoma of cortex of right adrenal glands, 10 by 12 cm.; 600 Gm. (operation)	Six months postoperative, felt well; appeared as prior to illness; obesity and hirsutism gone; menses and blood pressure normal
Right adrenal gland half normal size; left, tumor 6 by 4 by 2 cm.; cortical adenoma (operation)	After operation, lost 31 pounds (14 Kg.); menses ceased; hirsuties disappeared; basal metabolic rate −9; blood pressure 98/62
Right adrenal gland normal; left, 2.7 by 2 by 5 cm. adenocarcinoma, weight 5.4 Gm. (operation)	Two months postoperative, face normal; blood pressure 130/76; stronger
Marked enlargement of adrenal glands; cortical hyperplasia; no adenoma (operation, part of each gland removed)	Four months postoperative, face less swollen; diet unrestricted and no glycosuria
Pituitary gland normal (serial sections made); tumor of thymus "thymoma," 5 cm. in diameter; adrenal glands very large, combined weight 49 Gm.; ribs friable and could be broken easily with fingers	Friedman reaction negative; serum proteins, 4.2 Gm. per hundred cubic centimeters
Pituitary gland showed increase in basophil cells, one collection 0.3 mm. in diameter; carcinoma of cortex of left adrenal gland; right normal; gonads atrophic; osteoporosis "extreme" +++; death after adrenalectomy	Authors consider it "doubtful" if the collection of basophilic cells in hypophysis could be considered an adenoma
Carcinoma of cortex of right adrenal gland, weighing 1,350 Gm.; death 24 hours after removal of carcinoma of adrenal cortex	Author expressed the belief that pituitary basophilism might have been associated with and even the cause of the tumor of the adrenal glands; autopsy not permitted
Pituitary gland normal (serially sectioned); hypertrophy of thyroid gland; parathyroid bodies normal; oat cell carcinoma of thymus gland 6.2 by 4.8 by 2.5 cm.; pancreas "not definitely abnormal" adrenal glands enlarged; combined weight 44.3 Gm.; practically no medulla; all cortex; active spermatogenesis; combined weight of gonads 27.9 Gm.; no osteoporosis; death caused by respiratory obstruction (cellulitis of neck)	
Pituitary gland normal (not examined by serial sections); thyroid gland hyperplastic; oat cell carcinoma of thymus gland 3.7 by 3 by 1.5 cm.; pancreas normal; enlargement of adrenal glands, especially of cortex, combined weight 20.6 Gm., normal histology; death from hypoglycemia (?)	
Pituitary gland enlarged, much colloid, no mention of serial sections; adenomatous hyperplasia of thyroid gland, colloid present; thymus gland replaced by fat; pancreas normal; adrenal glands hypertrophic, patch of perivascular lymphocytic infiltration in medulla; gonads enlarged, fibrotic; death caused by heart failure and nephritis	Oat cell carcinoma 1 cm. in diameter found in lungs, with histologic picture exactly like that of those found in thymus gland in cases 12 and 13

* Diet restricted in carbohydrate.

TABLE 3.—*Methods of Administration of Roentgen Therapy*

Number	Author	Sex	Age at Onset	Duration of Illness, Years	Clinical Observations Prior to Roentgen Therapy: Obesity	Amenorrhea	Impotence	Hirsutism	Striae	Glycosuria	Basal Metabolic Rate	Blood Pressure	Skeletal Decalcification	Interval Between Treatments, Months	Roentgen Therapy to Hypophysis: Factors of Treatment: Kilovolts	Filter: Milliamperes	Filter: Copper, Thickness, Mm.	Filter: Aluminum, Thickness, Mm.	Focal Skin Distance, Cm.	Time, Minutes	Ports	Number of Days Treatment Occupied	Total Number of Roentgen Units
Verified Cases																							
1	Cushing [6] (Miss P.)	F	20	13	Face	+	..	++	++	..	—40 — 1	240	Atrophy of vertebrae; fractures	..	185	..	½	1	40 to 46	..	2	4	1,220
2	Kepler [6a]	F	30	5	Neck, trunk abdomen	+	..	+	+	+	—10 —20	160/120	Spine, skull, pelvis	.. 1	200 200	5 5	¾ ¾	1 1	50 50	60 60	3* 3*	3 3	1,440 1,440
3	Marburg, O.: Arb. a. d. neurol. Inst. a. d. Wien. Univ. **35**: 143, 1933	M	23	..	Face, abdomen	..	+	..	+	+	—28	Elevated	Skull	..	†	..	..	..	..	..	..	..	.....
4	Craig, J., and Cran, G. S.: Quart. J. Med. **3**: 57 (Jan.) 1934	F	24	4	Abdomen, thighs, upper part of arms	+	..	+	+	0	....	180/118	+	..	†	..	..	..	..	..	..	..	.....
5	Wright, C. A.: M. Rec. **141**: 191 (Feb. 20) 1935	M	10	1½	Face, neck, trunk	..	..	..	+	0	—18	154/110	Thin vertebrae	.. 2	210 210	5 5	1 1	.. ..	50 50	240 240	2 2	16 18	3,000 3,000
6	Freyberg and others	M	12	7	Face, neck, trunk	..	+	0	+	0	— 3 —12 —24	155/125	+++	..	200	30	½	1	50	3.3	2	5	1,600
Clinical Diagnoses: Patients Living when Case was Reported																							
7	Cushing [1] (E. G. F.)	M	25	7	Abdomen	..	+	Loss of hair	+	+	+10 — 1 —10	165/ 70 178/100	0	..	185	..	½	1	40	...	2	4	760
8	Cushing [8] (Alice D.)	F	8	7	Face, neck, trunk	+	..	+	+	+	—28 —33 —22	140/110 180/110	Marked	.. 1½ 2 3 4 8 2 2	185 185 185 185 185 185 185 185	.. ..	½ ½ ½ ½ ½ ½ ½ ½	1 1 1 1 1 1 1 1	40 to 46 Same Same Same Same Same Same Same	... ...	2 2 2 2 2 2 2 2	6 5 4 4 4 4 4 4	1,000 1,000 1,200 1,120 1,200 1,200 1,200 1,200
9	Kepler [6a]	F	23	4	Abdomen	0	..	+	+	..	— 9	Elevated	Marked	..	200	5	¾	1	50	60	4	4	1,920
10	Pardee, I. H.: Arch. Neurol. & Psychiat. **31**: 1007 (May) 1934 Case 1	F	16	14	Abdomen	0	..	+	+	..	—15	150/110	Skull	..	†	..	..	..	..	..	..	..	.....
11	Case 2	F	23	1	General	+	..	+	+	0	— 7	Normal	Atrophic vertebrae	..	†	..	..	..	..	..	..	..	.....
12	Case 3	F	37?	..	General	..	..	+	+	..	+ 5	170/ 90	0	..	†	..	..	..	..	..	..	..	.....
13	Wall, C.: Proc. Roy. Soc. Med. **27**: 395 (Feb.) 1934	F	15	5	General	+	..	+	+	0	....	160/110 185/125	0	..	†	..	..	..	..	..	..	..	.....
14	Pritchard, E. A. B.: Proc. Roy. Soc. Med. **27**: 673 (April) 1934	F	26	14	+	0	..	+	..	0	....	190	.....	..	†	..	..	..	..	..	..	..	.....
15	Lawrence, R. D.: Proc. Roy. Soc. Med. **27**: 275 (Jan.) 1934	F	33	4	+	+	..	+	..	..	....	160/110 170/125	+	.. 3	180 180	.. ..	½ ½	1 1	45 45	.. ..	2 2	25 24	3,800 1,750
16	Jamin, F.: München. med. Wchnschr. **81**: 1045 (July 13); 1085 (July 20) 1934	M	13	1	+	..	..	+	+	+	—10	125/ 85 210/130	Marked; "fish spine"	..	200	6	½	..	46	..	3	4	1,400‡
17	Wright, C. A.: M. Rec. **141**: 191 (Feb. 20) 1935 Case 2	F	?	?	+	§	#	+	+	..	— 8	180/128 230/128	Marked; spine and skull	.. 2	210 210	5 5	¾ ¾	1 1	.. ..	240 240	2 2	16 31	3,000‡ 3,000‡
18	Wohl, M. G.; Moore, J. R., and Young, R.: Radiology **24**: 53 (Jan.) 1935	F	20	3	+ 232 pounds (105 Kg.)	¶	..	Slight	+	0	—26	140/ 85 155/ 90	Areas of rarefaction in tibia, metatarsals and phalanges	..	160 av. 218 pk.	..	½	1	50	...	2	49	1,500

* Roentgen therapy given to the thymic region also.
† Factors of treatment not known.
‡ As nearly as could be calculated from the factors known.
§ Scanty menses.
# Frigid.
¶ Scanty irregular menses.

Interval After Roentgen Therapy	Clinical Observations After Roentgen Therapy	Comment
1 mo.	.....	"No immediate effects of any appreciable kind;" death 1 month after treatment (acute pulmonary edema)
1 mo.	.....	"No material change;" adrenal glands normal at time of surgical exploration
10 mo. (approximately)	.....	No knowledge of change; death within 1 year after first roentgen therapy was given
3 yr.	.....	No knowledge of change; death 3 years after roentgen therapy
4 mo.	.....	No mention made of any improvement; death 4 months after therapy (purulent bronchitis and empyema)
5 mo.		
3 mo.	Blood pressure, 160/132.....	"Definite improvement; patient felt better and stronger; no headaches; no backache except on motion; less plethora;" death 3 months after last treatment (laparotomy)
6 mo.	No change in obesity; impotence persisted; no hirsutism; striae, the same as before; no glycosuria; blood pressure 160/130 and 175/135; no change in skeletal decalcification	No change was noted after roentgen therapy; death 6 months after therapy following exploratory operation of left adrenal gland
1 yr.	Glycosuria disappeared; patient on general diet at time of last report	"Almost immediate striking improvement in strength and resistance to infection"; (Dr. Woodyatt stated that he was "skeptical of influence of radiotherapeusis in this case")
4 mo.	Apparent diminution of hirsutism; increasing striae; continued to gain weight	Became alert and interested in life; far better than she had been for a long time; improvement chiefly in sense of well-being; less plethora
2½ mo.		
1 yr.	Obesity disappeared; normal menses were present; hirsutism disappeared; blood pressure became normal	"Is enjoying excellent health"
4 mo.	.....	"No material change so far as I have been able to learn" (adrenal glands appeared normal at surgical exploration)
1 yr.	.....	"Less fatigue and infection"
?	Return of menses.....	No other change
1+ yr.	.....	Improvement of headaches
1½ yr.	Obesity disappeared except on face; amenorrhea persisted; no change in hirsutism; striae were more marked; no glycosuria; blood pressure 170/115; no skeletal decalcification	Besides roentgen therapy the patient received thyroid extract and strict diet
2 yr.	Obesity less, most on shoulders and chest; amenorrhea since roentgen therapy; hirsutism increased, ++; no glycosuria; blood pressure same; large bones showed rarefaction	Disappearance of polyuria since roentgen therapy; laparotomy 2 years prior to therapy revealed normal right adrenal gland and pelvic organs
7 mo.		
4 mo.	Obesity disappeared; menses began; hirsutism less; only occasional trace of glycosuria; blood pressure 124/85; skeletal decalcification improved	Disappearance of leg pains, bruising, thirst, hunger and slight exophthalmos; retinal hemorrhages and exudate less; general weakness unchanged; diet of 100 Gm. of carbohydrate needed 40 units of insulin prior to therapy; after therapy 150 Gm. carbohydrate satisfactory without insulin
2 mo.	Obesity disappeared; striae became paler; blood pressure 165/65 and 110/70	Great improvement in strength; prior to therapy could not stand alone; after therapy could climb stairs alone
8 mo.	Obesity absent; no hirsutism; striae pale and atrophic; no glycosuria; basal metabolic rate, +16; blood pressure 110/75 and 125/85; much improvement in skeletal decalcification	Felt entirely well at time of report; kyphosis was only recognizable remnant of previous syndrome; normal activity and growth
7 mo.		
4½ mo.	Libido returned; hirsutism less; blood pressure 220/160; marked increase in density of spine	"Much improved; less plethora; headaches less severe; weakness persists; ecchymoses occur"
2 mo.	Obesity reduced; blood pressure decreased; areas of rarefaction smaller, new bone formed	"General condition promptly improved"; leg pain decreased
11 mo.	Weight reduced to 187 pounds (80.8 Kg.); normal menses; blood pressure 140/90; scarcely any defects in the bones	Patient received a 1,500 calory diet and desiccated thyroid, 1 grain three times a day; therefore, difficult to evaluate results of roentgen therapy

clinically as examples of pituitary basophilism; in both the pituitary gland (serial sections in one case) was found to be normal, and in each a carcinoma of cortical adrenal origin was found. Kepler [6] and Walters [12] reported a series of cases in which there were clinical manifestations similar to Cushing's syndrome and the patient was apparently cured by surgical removal of a cortical suprarenal adenoma or of portions of hyperplastic adrenal glands.

In table 2 are listed the salient features of all reported cases which have come to our attention in which the condition clinically simulated pituitary basophilism, and in which lesions considered to be the cause of the syndrome have been found elsewhere than in the hypophysis. Only those cases in which there was histologic verification have been included. In the first eleven cases the causative lesion was ascribed to a neoplasm or to atrophy of the adrenal glands. In cases 12 and 13 the malady was ascribed to an oat cell carcinoma of the thymus. (A thymoma also occurred in case 9). In the fourteenth case, besides the hypertrophic adrenal glands, an oat cell carcinoma was found in the lungs. In cases 4, 9 and 12 the pituitary gland was examined by serial section and found to be normal. In the cases in which the patient was not examined post mortem it is possible, of course, that pituitary lesions may have existed. Cases 5, 6, 7 and 8, in patients who were living when the cases were reported, were included in the group because of the proof of adrenal abnormality by examination of material obtained at surgical operation and especially because of the improvement following the removal of an adrenal neoplasm or of part of a hyperplastic adrenal gland.

It should be noted that, although the significant lesion in some cases was thought to be a neoplasm of the thymus gland, in all these cases adrenal hypertrophy, especially of the cortex, existed.

It is seen, then, that there are on record cases of "multiglandular disease" exhibiting similar clinical syndromes, in some of which the pituitary gland was proved to be normal at postmortem examination, and a lesion was found in the adrenal glands. Other cases have been reported in which there were normal adrenal glands and proved hypophyseal basophilism. The difficulty of making a correct clinical diagnosis in some cases is evident. Roentgenograms of the sella turcica are of no help in differentiating these conditions, for the pituitary lesion, when it exists, is usually so small that changes of the bones are not produced. When no direct indication of adrenal lesion is present (palpable tumor or distorted pyelograms), one has no means of definitely locating the lesion responsible for the syndrome.

12. Walters, W.; Wilder, R. M., and Kepler, E. J.: Progress Subsequent to Subtotal Bilateral Suprarenalectomy for the Suprarenal Cortical Syndrome, Proc. Staff Meet., Mayo Clin. **9**:661 (Oct. 31) 1934. Walters and others.[6c]

It seems wise in cases in which the causative lesion cannot be definitely learned to treat the patient for pituitary basophilism and to administer roentgen therapy to the pituitary gland. If no benefit results, certainly the adrenal glands should be explored, and any abnormality found should be treated as the conditions indicate. This plan of treatment seems most wise, especially since patients with pituitary basophilism are peculiarly susceptible to infection and are therefore poor surgical risks.

ROENTGEN THERAPY IN CASES OF PITUITARY BASOPHILISM

Data on all the known cases of pituitary basophilism in which roentgen therapy has been applied to the hypophysis are tabulated in table 3. The original clinical findings, the details of therapy and the results obtained are noted.

Wright's case (5) is the only one in which the diagnosis of basophilism has been verified in which the condition was reported to be improved after roentgen therapy. The improvement in this patient was chiefly in the state of general well-being. The blood pressure was higher after treatment than before. Changes in many of the cardinal features of the disease are not mentioned.

Of the unverified cases, the condition in that of Kepler (case 9) and in that of Pritchard (case 14) was not improved by roentgen therapy. Improvement in only one symptom was reported for each of Pardee's patients (cases 10, 11 and 12), and certainly no dramatic results were reported in any of his cases. In Wall's patient (case 13), obesity disappeared, but the strict diet and thyroid medication could very well account for this improvement. Wohl's patient (case 18) showed reduction in weight, return of regular menses and an improved skeleton, but in this patient too the reduction diet and thyroid medication make it difficult to evaluate roentgen therapy. In the remainder of the cases the condition was reported as improved.

In some cases the improvement was marked. A most gratifying result from roentgen therapy was noted in the case reported by Jamin (case 16). A boy aged 14 showed a rapid development of Cushing's syndrome and a rapid return to normal following roentgen therapy directed to the hypophysis. Within two months his appearance was again almost normal, the blood pressure returned to normal and his strength improved, so that he could walk about and climb stairs (previous to therapy he could not stand alone). Within eight months he was able to ride long distances on a bicycle and to enter into all activities with his companions.

Almost as dramatic is the case of Alice D. (case 8), one of Cushing's patients. She did not improve as rapidly as did Jamin's patient; however, persistence in treatment was rewarded by a return to normal

appearance and disappearance of hypertension. Cushing [13] reported this patient to be in "excellent health" at the time of this writing (one year after the last roentgen treatment).

Table 3 lists instances in which roentgen therapy as given was of no value and others in which apparent cure was effected. This wide variation in results is interesting and might be explained by the combined effect of several contributing factors. It is most likely that different basophil adenomas vary in their sensitivity to the roentgen rays. Jamin's patient, for instance, who showed marked and rapid improvement, received practically the same dose of roentgen therapy, given with similar factors, as did our patient, who showed no sign of improvement in six months. The age of the patient may be a factor, but it does not seem to be of major importance. The two patients showing the greatest improvement were only 14 and 15 years of age, but Lawrence's patient (case 15) was 37 years of age. It may be that the duration of illness before roentgen therapy is instituted is a factor. The patients exhibiting recognizable features of Cushing's disease for 13 or 14 years (cases 1 and 14) were not benefited by roentgen therapy.

The method of administering roentgen therapy and the amount of irradiation appear to be especially important factors and should receive careful consideration. In every case listed in table 3 in which large amounts of roentgen rays were applied to the hypophysis the condition was markedly improved. The patient in case 8 was given repeated treatments, each of moderate size. In cases 5, 15 and 17 more intensive and fewer treatments were given with good results. The failure of roentgen therapy in our case and in other reported cases might very well be explained by the fact that this treatment was not sufficiently pursued or that the dosage was insufficient. It would seem that much can be done for these patients if roentgen therapy in sufficient doses is persistently applied.

SUMMARY

A verified case of pituitary basophilism showing the classic clinical syndrome has been reported.

The essential features of other verified cases reported since Cushing's review (1933) have been summarized.

The resemblance of the clinical manifestations of other lesions, especially cortical adrenal neoplasm or hyperplasia, to "Cushing's syndrome" of pituitary basophilism has been pointed out.

The results of roentgen therapy directed to the hypophysis in cases of Cushing's disease have been reviewed. This study indicates that roentgen therapy should be intensively and persistently pursued in cases of pituitary basophilism.

13. Cushing, H.: Personal communication to the authors.

CALCIUM AND PHOSPHORUS METABOLISM IN A VERIFIED CASE OF PITUITARY BASOPHILISM

R. H. FREYBERG, M.D.
AND
R. LORIMER GRANT, PH.D.
ANN ARBOR, MICH.

Patients with pituitary basophilism commonly have generalized demineralization of the skeleton. In some cases this is so severe that multiple fractures occur. The cause of this skeletal abnormality has been obscure. Cushing [1] suggested that the parathyroid bodies might be activated to excessive secretion by the pituitary lesion and thus cause the osteoporosis.

In the majority of verified cases of pituitary basophilism the parathyroid glands when examined post mortem are described as being normal, fatty or atrophic. In several cases the parathyroid glands were enlarged but were found to be grossly infiltrated with fat, which contributed to their size. In only one case has a parathyroid adenoma been found.[2] Only in the case described in 1912 by Schmorl [3] and later by Molineus [4] has hyperplasia of the parathyroid glands been observed. The patient exhibited the clinical syndrome of pituitary basophilism and at postmortem examination was found to have a large basophil adenoma of the hypophysis, oxyphilic hyperplasia of the parathyroid bodies without adenomatous formation and "brown tumors" of the bone. The relationship of the pituitary and parathyroid lesions in this case is not clear.

In the present state of our knowledge, it is hazardous to interpret the functional behavior of the parathyroid glands from their histologic appearance. It would seem, therefore, that a study of the calcium and

---

The expense of this investigation was defrayed in part by Parke, Davis & Co.

From the Department of Internal Medicine, Medical School, University of Michigan.

1. Cushing, H.: "Dyspituitarism": Twenty Years Later, with Special Considerations of the Pituitary Adenomas, Harvey Lectures, 1932-1933, Baltimore, Williams & Wilkins Company, 1934, p. 90.

2. Since these data were compiled, a case of verified pituitary basophilism has been reported by J. A. Lawrence and H. M. Zimmerman (Pituitary Basophilism: Report of a Case, Arch. Int. Med. **55**:745 [May] 1935), in which one parathyroid body contained an adenoma.

3. Schmorl, G.: Gesellschaft für Natur und Heilkunde zur Dresden, offizielles Protokoll, München. med. Wchnschr. **59**:2887, 1912.

4. Molineus: Ueber die multiplen brauen Tumoren bei Osteomalacie, Arch. f. klin. Chir. **101**:333, 1913.

phosphorus metabolism would be a more reliable approach to an understanding of the fundamental disturbance responsible for the skeletal changes. Such studies of the mineral metabolism in pituitary basophilism have been very meager. Aub studied two of Cushing's [5] cases, but only while the patients had a low intake of calcium. In one case there was normal elimination of both calcium and phosphorus; in the other there was increased excretion of calcium in the urine. The urinary phosphorus, however, was not increased. The only other studies of mineral metabolism reported are those of Wall,[6] who observed the calcium and phosphorus exchange over a period of six days in an unverified case of pituitary basophilism, while the intake of calcium was low.[7] Several investigators have reported the calcium and phosphorus concentration of the serum in cases of Cushing's disease. The results of all these studies of calcium and phosphorus metabolism are presented in table 1.

The purpose of this communication is to report studies of the calcium and phosphorus metabolism made over a long period in a verified case of pituitary basophilism. A complete account of the clinical and pathologic findings in this case have been reported elsewhere.[8] Roentgenograms of this patient, Z. K., demonstrated an extreme degree of generalized skeletal demineralization without the formation of cysts, a typical "fish spine," fragmentation of the heads of the femurs and metatarsal bones and nonunion of many epiphyses.

The mineral metabolism was studied for three months. The patient then received roentgen therapy to the pituitary gland, and, after an interval of two months, the calcium and phosphorus exchange was again observed for a period of eleven weeks.

OBSERVATIONS ON THE PATIENT

Method.—Studies of the calcium, phosphorus and nitrogen balance were carried out while the patient was receiving diets of different calcium and phosphorus content and while he was receiving various supplements. One and five-tenths liters of distilled water were given daily. The ingesta and all excreta were quantitatively analyzed for calcium, phosphorus and nitrogen, and the exchange was calculated on

5. Cushing, H.: Further Notes on Pituitary Basophilism, J. A. M. A. **99**:281 (July 23) 1932. Cushing.[1]

6. Wall, C.: Adreno-Genital Syndrome (Cushing Type), Proc. Roy. Soc. Med. **27**:395 (Feb.) 1934.

7. The calcium metabolism was studied in the case recently reported by Lawrence and Zimmerman [2] and found not to show the usual picture of hyperparathyroidism.

8. Freyberg, R. H.; Barker, P. S.; Newburgh, L. H., and Coller, F. A.: Pituitary Basophilism (Cushing's Syndrome): Report of a Verified Case, with a Discussion of the Differential Diagnosis and Treatment, Arch. Int. Med., this issue, p. 187.

TABLE 1.—*Calcium and Phosphorus Data on Cases of Pituitary Basophilism Taken from Literature*

Author	Clinical Diagnosis	Pathologic Diagnosis	Osteoporosis	Serum			Calcium Exchange (3 Day Periods)					Phosphorus Exchange (3 Day Periods)				
				Calcium, Mg. per 100 Cc.	Phosphorus, Mg. per 100 Cc.	Phosphatase, Units per 100 Cc.		Intake, Gm.	Urine, Gm.	Feces, Gm.	Total Excretion, Gm.	Balance, Gm.	Intake, Gm.	Urine, Gm.	Feces, Gm.	Total Excretion, Gm.	Balance, Gm.
Cushing [1] (Miss P.)	Pituitary basophilism	Basophilic adenoma of adenohypophysis	Slight	Normal	Normal	Normal	Normal elimination of both calcium and phosphorus									
Cushing [5] (Alice D.)	Pituitary basophilism	Living at time of report	++	9.8	2.7	....	I	0.30	0.65	0.27	0.92	−0.62	1.86	0.87	0.47	1.34	0.52
							II	0.30	0.84	0.48	1.32	−1.02	1.86	0.75	1.08	1.83	0.03
							Av.	0.30	0.74	0.37	1.11	−0.81	1.86	0.81	0.77	1.58	0.28
Wall [6]	Adrenogenital syndrome (Cushing type)	Living at time of report	None	10.4	2.8	....	I	0.31	0.42	0.79	1.21	−0.90					
							II	0.31	0.55	0.61	1.16	−0.85					
							Av.	0.31	0.48	0.70	1.19	−0.88					
Craig, J., and Cran, B. S.: Quart. J. Med. **3**: 57 (Jan.) 1934	Basophilic adenoma of pituitary	Basophilic adenoma of anterior lobe of pituitary body	+	10.8	2.01	....											
Wright, C. A.: M. Rec. **141**: 191 (Feb. 20) 1935	Pituitary basophilism	Basophine pituitary adenoma	Thin vertebrae	9.8	9.0	....											
Rutishauser, E.: Deutsches Arch. f. klin. Med. **175**: 640, 1933	Osteoporotic obesity	Increase in basophils with adenoma-like hyperplasia	++	10.0	2.5	....											
Kepler, E. J.: Proc. Staff Meet., Mayo Clin. **8**: 102 (Feb. 15) 1933	Polyglandular dyscrasia	Normal adrenal glands at operation; living at time of report	Skull, spine, ribs; multiple fractures	9.6	2.64	11.4											
Lawrence, R. D.: Proc. Roy. Soc. Med. **27**: 275 (Jan.) 1934	Cushing's pituitary basophilism	Living at time of report	+ Fractured ribs and os pubis	9.7	2.0	0.5-0.6											
Wohl, M. G.; Moore, J. R., and Young, B. R.: Radiology **24**: 53 (Jan.) 1935	Basophilic adenoma	Living at time of report; improved by roentgen therapy to pituitary	None of spine and ribs; areas of rarefaction in metatarsal bones, phalanges and right tibia	11.5	4.0	....											

the basis of three day metabolism periods. Whenever the nitrogen balance was negative, the intake of calcium and phosphorus was corrected by the amount of these elements liberated by the destruction of tissue. At frequent intervals determinations of serum calcium and phosphorus were made.[9]

First Study.—Results of the study are presented in table 2. In figures 1 and 2 the calcium and phosphorus exchange and the concentration of these elements in the serum are plotted for the first forty three day periods.

Throughout this first metabolism study, the diet was made undernourishing (890 calories) in order to reduce the patient's weight. The calcium content of

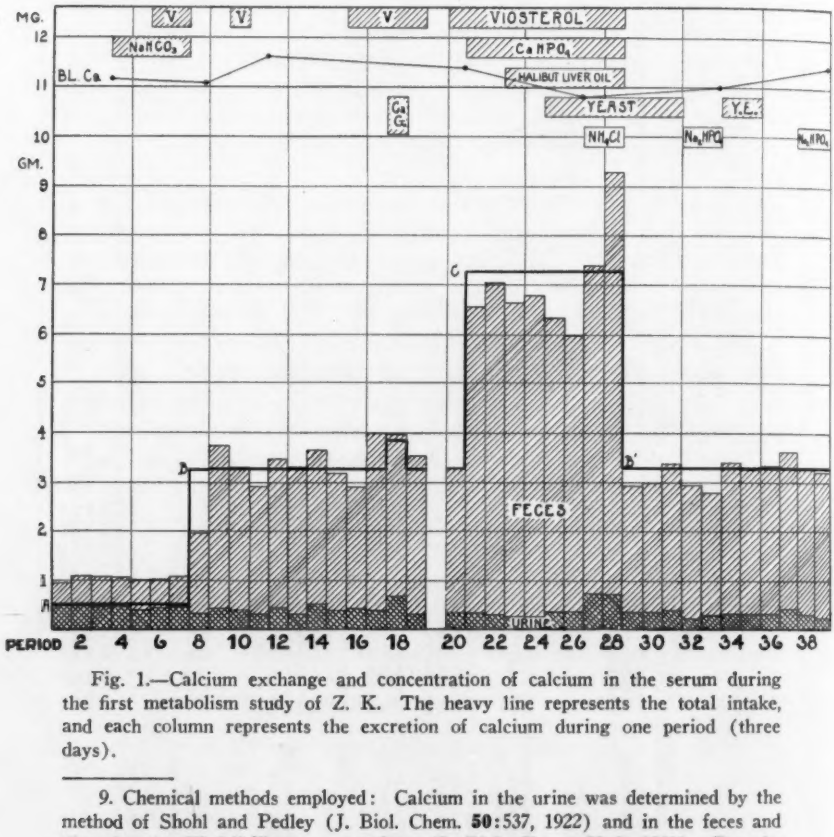

Fig. 1.—Calcium exchange and concentration of calcium in the serum during the first metabolism study of Z. K. The heavy line represents the total intake, and each column represents the excretion of calcium during one period (three days).

9. Chemical methods employed: Calcium in the urine was determined by the method of Shohl and Pedley (J. Biol. Chem. **50**:537, 1922) and in the feces and diets by the Tisdall-Kramer procedure (J. Biol. Chem. **48**:1, 1921). For the estimation of serum calcium, the Clark-Collip (J. Biol. Chem. **63**:461, 1925) modification of the Tisdall method was used. The methods of Fiske and Subbarow (J. Biol. Chem. **66**:375, 1925) were employed for all phosphorus determinations. All nitrogen analyses were made by the Kjeldahl method. Titratable acidity of the urine was measured by the method of Henderson and Palmer (J. Biol. Chem. **17**:305, 1914). Urinary ammonia was determined by the Folin-Bell (J. Biol. Chem. **29**:329, 1917) method.

TABLE 2.—*First Study of Calcium and Phosphorus Metabolism in Patient Z. K.*

TABLE 2.—*First Study of Calcium and Phosphorus Metabolism in Patient Z. K.*

Diet	Period	Medication	Nitrogen			Total Urinary Acid,*	Calcium					Phosphorus				
			Intake, Gm.	Output, Gm.	Balance, Gm.	Cc. N/10 Acid	Intake, Gm.	Urine, Gm.	Feces, Gm.	Total Excretion, Gm.	Balance, Gm.	Intake, Gm.	Urine, Gm.	Feces, Gm.	Total Excretion, Gm.	Balance, Gm.
Low calcium 890 calories; calcium-phosphorus ratio 0.46	1	.....	15.1	13.67	1.43	1,546	0.49	0.47	0.48	0.94	—0.45	1.06	Lost		....	.....
	2	.....	15.1	17.86	—2.76	1,421	0.50	0.47	0.62	1.09	—0.59	1.22	1.28	0.62	1.90	—0.68
	3	.....	15.1	17.32	—2.22	1,308	0.50	0.45	0.63	1.08	—0.58	1.19	1.22	0.52	1.74	—0.55
	4	Sodium bicarbonate 3.84 Gm.....	15.1	17.34	—2.24	830	0.50	0.44	0.61	1.05	—0.55	1.19	1.08	0.60	1.68	—0.49
	5	Sodium bicarbonate 11.52 Gm.....	15.1	16.20	—1.1	209	0.49	0.39	0.61	1.0	—0.50	1.12	0.94	0.67	1.61	—0.49
	6	Sodium bicarbonate 17.28 Gm., viosterol †	15.1	14.72	0.38	—390	0.49	0.42	0.60	1.02	—0.53	1.06	Lost	0.67	....	.....
	7	Sodium bicarbonate 17.52 Gm., viosterol †	15.1	17.17	—2.03	—489	0.50	0.44	0.62	1.06	—0.56	1.17	1.07	0.70	1.77	—0.59
High calcium diet, 890 calories; calcium-phosphorus ratio 1.31	8	.....	16.95	17.07	—0.12	474	3.26	0.34	1.60	1.94	1.32	2.50	1.07	1.17	2.24	0.26
	9	.....	16.95	18.35	—1.4	897	3.28	0.41	3.30	3.71	—0.43	2.57	1.21	1.94	3.15	—0.58
	10	Viosterol †.....	16.95	19.87	—2.92	1,018	3.28	0.38	2.89	3.27	0.01	2.66	1.61	1.69	3.30	—0.64
	11	.....	16.95	19.47	—2.52	1,161	3.28	0.32	2.57	2.89	0.39	2.66	1.09	1.54	2.63	0.03
	12	.....	16.95	20.86	—3.91	1,024	3.28	0.42	3.00	3.42	—0.13	2.71	1.20	1.65	2.85	—0.13
	13	.....	16.95	20.87	—3.92	1,089	3.28	0.32	2.99	3.31	—0.02	2.71	1.32	1.59	2.91	—0.19
	14	.....	16.95	20.82	—3.87	1,094	3.28	0.48	3.13	3.61	—0.32	2.71	1.28	1.78	3.06	—0.35
	15	.....	16.95	20.12	—3.17	1,106	3.28	0.36	2.82	3.18	0.10	2.67	1.19	1.31	2.50	0.17
	16	Viosterol †.....	16.95	19.64	—2.69	1,270	3.28	0.40	2.47	2.87	0.41	2.64	1.10	1.60	2.70	—0.05
	17	Viosterol †.....	16.95	19.94	—2.99	883	3.30	0.37	3.61	3.98	—0.68	2.66	1.02	2.16	3.18	—0.52
	18	Viosterol † + Intravenous injection of calcium gluconate (0.54 Gm. calcium).....	16.95	20.50	—3.55	1,026	3.84	0.67	3.28	3.95	—0.11	2.69	1.07	1.66	2.73	—0.04
	19	.....	16.95	19.36	—2.41	921	3.30	0.28	3.21	3.49	—0.19	2.63	1.07	1.79	2.86	—0.23
	20	.....	16.95	17.43	—0.48	789	3.28	0.34	2.92	3.26	0.02	2.52	0.95	1.76	2.71	—0.19
	21	Viosterol † + 14.3 Gm. $CaHPO_4$	17.45	16.98	0.47	1,364	7.24	0.34	6.22	6.56	0.68	5.28	1.27	3.66	4.93	0.35
	22	Viosterol † + 14.3 Gm. $CaHPO_4$	17.45	19.11	—1.66	1,210	7.24	0.28	6.74	7.02	0.22	5.38	1.32	4.10	5.42	—0.04
	23	Viosterol † + 14.3 Gm. $CaHPO_4$ + Halibut liver oil‡	17.68	19.1	—1.42	1,218	7.24	0.25	6.36	6.61	0.63	5.36	1.25	3.51	4.76	0.70
	24	Viosterol † + 14.3 Gm. $CaHPO_4$ + Halibut liver oil‡	17.68	18.62	—0.94	1,248	7.24	0.23	6.53	6.76	0.48	5.34	1.36	3.30	4.66	0.68
	25	Viosterol † + 14.3 Gm. $CaHPO_4$ + Halibut liver oil‡ + 9 cakes compressed yeast.....	19.98	20.31	—0.33	1,247	7.24	0.36	5.93	6.29	0.95	5.68	1.31	3.75	5.06	0.62
	26	Viosterol † + 14.3 Gm. $CaHPO_4$ + Halibut liver oil‡ + 9 cakes compressed yeast.....	19.98	21.77	—1.79	1,035	7.24	0.36	5.60	5.96	1.28	5.76	1.55	2.61	4.16	1.60
	27	Viosterol † + 14.3 Gm. $CaHPO_4$ + Halibut liver oil‡ + 9 cakes compressed yeast and	25.51	22.92	2.59	2,727	7.24	0.73	6.65	7.38	—0.14	5.66	1.85	3.01	4.86	0.80
	28	Viosterol † + 14.3 Gm. $CaHPO_4$ + Halibut liver oil‡ + 18 Gm. ammonium chloride...	25.51	30.09	—4.58	3,453	7.25	0.71	8.52	9.23	—1.98	5.92	1.85	4.59	6.44	—0.52
	29	9 cakes compressed yeast.....	19.25	23.86	—4.61	2,463	3.29	0.35	2.55	2.90	0.39	3.14	1.17	1.50	2.67	0.47
	30	9 cakes compressed yeast.....	19.25	21.35	—2.1	1,373	3.28	0.35	2.64	2.99	0.29	2.99	1.0	1.60	2.60	0.39
	31	9 cakes compressed yeast.....	19.25	20.11	—0.86	1,013	3.28	0.38	2.98	3.36	—0.08	2.92	1.04	1.66	2.70	0.22
	32	2 Gm. di-sodium hydrogen phosphate.....	17.1	16.94	0.16	928	3.28	0.21	2.72	2.93	0.35	2.86	1.09	1.27	2.36	0.50
	33	2 Gm. di-sodium hydrogen phosphate.....	17.08	16.42	0.66	817	3.28	0.27	2.49	2.76	0.52	2.86	1.20	1.25	2.45	0.41
	34	Yeast extract.....	17.35	17.73	—0.38	857	3.28	0.28	3.10	3.38	—0.10	2.61	0.95	1.78	2.73	—0.12
	35	Yeast extract.....	17.35	17.64	—0.31	917	3.28	0.29	2.95	3.24	0.04	2.60	1.06	1.25	2.31	0.29
	36	.....	16.95	17.96	—1.01	999	3.28	0.32	2.98	3.30	—0.02	2.55	1.03	1.65	2.68	—0.13
	37	.....	16.95	17.83	—0.88	1,069	3.28	0.40	3.18	3.58	—0.30	2.54	0.99	1.75	2.74	—0.20
	38	10.8 Gm. di-sodium hydrogen phosphate..	17.29	17.54	—0.25	954	3.28	0.28	2.98	3.26	0.02	4.01	1.90	1.33	3.23	0.78
	39	10.2 Gm. di-sodium hydrogen phosphate..	17.4	17.79	—0.39	845	3.28	0.22	2.96	3.18	0.10	4.01	1.72	1.46	3.18	0.83
	40	.....	16.95	17.23	—0.28	953	3.28	0.22	3.03	3.25	0.03	2.51	0.86	1.74	2.60	—0.09

* Urinary ammonia plus titrable acidity.
† 1.2 Gm. of viosterol supplying 94,000 U. S. P. XI units of vitamin D per period.
‡ 3.6 Gm. halibut liver oil supplemented by viosterol, supplying 16,128,000 U. S. P. XI units of vitamin A and 27,700 U. S. P. XI units of vitamin D per period.

the serum was on the border line between a high normal value and a figure indicating slight hypercalcemia, and the phosphorus content was constantly below normal. The phosphatase content on one determination was found to be 5.1 Bodansky units.[10]

When the intake of calcium was low (periods 1 through 7), the amount of calcium in the urine was above the average excretion (0.19 Gm.) of normal persons on a similarly low calcium intake found by Bauer, Albright and Aub,[11] although the value is within the range of their normal values (0.03 to 0.47 Gm.). The total excretion of calcium per kilogram of body weight per period by our patient during the period of low calcium intake was 0.013 Gm., which is very

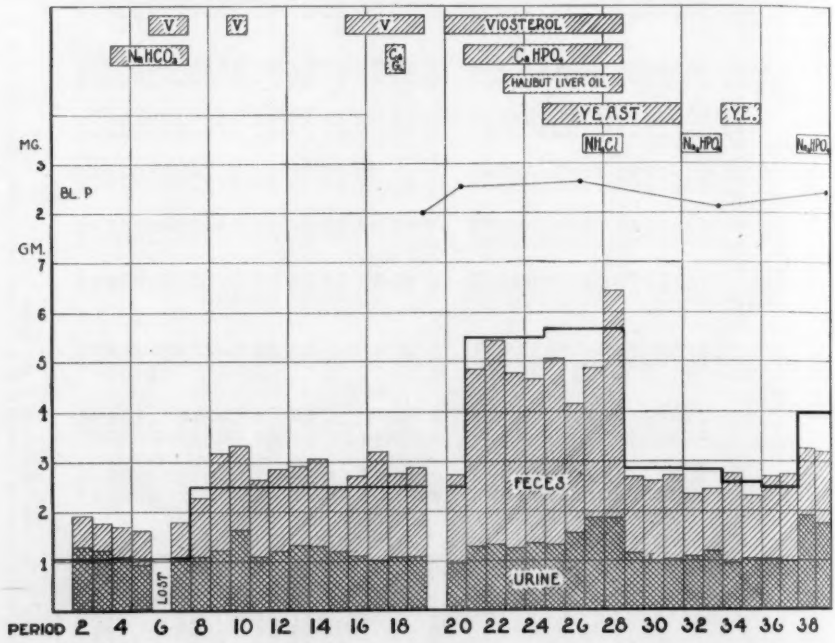

Fig. 2.—Phosphorus exchange and concentration of phosphorus in the serum during the first metabolism study of Z. K. The heavy line represents the total intake, and each column represents the excretion of phosphorus during one period (three days).

close to the average of 0.012 Gm. for the normal subjects studied by the aforementioned investigators. The urinary calcium did not decrease during periods 4, 5, 6 and 7, when large amounts of sodium bicarbonate were administered in order to make conditions optimal for minimal urinary excretion.

10. Dr. I. G. Macy made this analysis.

11. Bauer, W.; Albright, F., and Aub, J. C.: Studies of Calcium and Phosphorus Metabolism: II. The Calcium Excretion of Normal Individuals on a Low Calcium Diet; Also Data on a Case of Pregnancy, J. Clin. Investigation **7**:75 (April) 1929.

Beginning with period 8 and continuing throughout the remainder of the first study, a diet rich in calcium (800 Gm. of whole milk daily) was given. During periods 8 through 17 the urinary excretion of calcium actually decreased slightly, and the fecal excretion was high, averaging 2.97 Gm. per period, or 90 per cent of the intake. This high fecal excretion of calcium could have resulted from failure of absorption or from reexcretion of calcium into the intestine. In order to study this question, calcium gluconate was injected intravenously during period 18. In all, 0.54 Gm. of calcium equally divided in 12 injections was injected during the three day period. The amount of calcium excreted in the feces during this period did not increase. For this reason it is felt that the high amount of fecal calcium represents unabsorbed calcium. The urine for that period contained 0.67 Gm. of calcium, or 0.29 Gm. more than the average during the nine previous periods. The remainder of the injected calcium (0.25 Gm.) was retained. The phosphorus excreted during this period decreased by an amount almost exactly that needed to form tribasic calcium phosphate with the retained calcium.

It was evident from the study thus far that although the patient was in great need of calcium because of marked skeletal demineralization, when calcium was abundantly supplied in foods (especially milk), he absorbed only a small amount of this element. It was thought that a calcium salt, given as such, might be more readily absorbed. Accordingly, from periods 21 through 28, 14.3 Gm. of commercial di-calcium phosphate was ingested in each period, thus increasing the intake of calcium by 3.96 Gm. per period. Still only a small amount of calcium was absorbed, and the fecal excretion remained 90 per cent of the intake. The urinary excretion remained essentially unchanged.

Throughout the study large doses of irradiated ergosterol (proved to be potent by studies on rachitic rats) were of no value. Because of the reports of Macy and her associates[12] that positive calcium balance was effected in lactating women by the addition of cod liver oil and yeast to the diet, these supplements were fed. During the periods when yeast was first added, there was greater retention of calcium than at any other time. It was desired to determine whether this improvement resulted from the phosphorus or from the vitamin B that was contained in the yeast. Accordingly, these factors were studied separately while the patient received no calcium except that contained in the diet. During periods 32 and 33 di-sodium hydrogen phosphate was given in an amount sufficient to supply phosphorus equivalent to that in the yeast, and in periods 34 and 35 yeast extract supplying vitamin B equivalent to that in the yeast was administered. No definite benefit resulted from either supplement. Ammonium chloride administered during periods 37 and 38 produced an increase in excretion of calcium both in the urine and in the feces.

Several interesting features of the phosphorus exchange should be pointed out. When the phosphorus intake was low (periods 1 through 7) the excretion was not unusual, but when the dietary phosphorus was raised to 2.49 Gm. per period (beginning with period 8), the excretion of phosphorus in the urine remained unchanged, and the fecal excretion of this element was almost twice the urinary excretion. In general, the changes in the phosphorus exchange were similar to those observed in the exchange of calcium, except that when di-sodium hydrogen phosphate was given in abundance during periods 38 and 39, phosphorus was generously absorbed and retained.

---

12. Macy, I. G.; Hunscher, H. A.; McGosh, S. S., and Nims, B.: Metabolism of Women During the Reproductive Cycle: III. Calcium, Phosphorus, and Nitrogen Utilization in Lactation Before and After Supplementing the Usual Home Diets with Cod Liver Oil and Yeast, J. Biol. Chem. **86**:59 (March) 1930.

TABLE 3.—*Second Study of Calcium and Phosphorus Exchange of Z. K.*

Diet	Period	Medication	Nitrogen			Total Urinary Acid, Cc. N/10 Acid	Calcium					Phosphorus				
			Intake, Gm.	Output, Gm.	Balance, Gm.		Intake, Gm.	Urine, Gm.	Feces, Gm.	Total Excretion, Gm.	Balance, Gm.	Intake, Gm.	Urine, Gm.	Feces, Gm.	Total Excretion, Gm.	Balance, Gm.
Low calcium, 890 calories, calcium-phosphorus ratio 0.46	41		15.1	21.52	—6.42	1,572	0.51	0.32	0.60	0.92	—0.41	1.42	1.49	0.76	2.25	—0.82
	42		15.1	21.33	—6.23	1,475	0.51	0.42	0.43	0.85	—0.34	1.41	1.66	0.53	2.19	—0.78
	43		15.1	21.76	—6.66	1,824	0.51	0.30	0.59	0.89	—0.38	1.44	1.57	0.65	2.22	—0.78
	44	Intravenous injection of calcium gluconate (0.54 Gm. calcium)	15.1	20.31	—5.21	1,554	1.04	0.57	0.55	1.12	—0.08	1.36	1.15	0.65	1.80	—0.44
	45		15.1	19.80	—4.70	1,496	0.50	0.32	0.44	0.76	—0.25	1.33	1.48	0.61	2.09	—0.76
	46*		15.1	18.69	—3.59	1,503	0.50	0.29	0.66	0.95	—0.44	1.26	1.28	0.68	1.96	—0.70
High calcium, 890 calories, calcium-phosphorus ratio 1.31	47		16.98	19.19	—2.21	1,079	3.28	0.31	2.90	3.21	0.07	2.62	1.18	1.52	2.70	—0.08
	48		16.98	19.19	—2.21	1,125	3.28	0.51	2.33	2.84	0.44	2.62	1.32	1.51	2.83	—0.21
	49		16.98	19.89	—2.91	1,084	3.28	0.36	3.29	3.65	—0.37	2.66	1.10	2.37	3.47	—0.81
High calcium, 2,000 calories, calcium-phosphorus ratio 1.23	50		25.63	19.88	5.75	1,231	3.43	0.52	2.64	3.16	0.27	2.78	1.21	1.45	2.66	0.12
	51		25.63	19.52	6.11	1,010	3.43	0.68	2.91	3.59	—0.15	2.78	1.18	1.70	2.88	—0.10
	52		25.63	19.61	6.02	1,061	3.43	0.50	2.91	3.41	0.02	2.78	1.25	1.72	2.97	—0.19
	53		25.63	20.10	5.53	1,215	3.43	0.55	2.39	2.94	0.53	2.78	1.35	1.52	2.87	—0.09
	54	6 Gm. special viosterol†	25.63	19.67	5.96	1,191	3.43	0.60	2.53	3.13	0.30	2.78	1.37	1.24	2.61	0.17
	55	6 Gm. special viosterol†	35.63	20.57	5.06	1,193	3.43	0.57	2.95	3.52	—0.08	2.78	1.45	1.62	3.07	—0.29
	56	6 Gm. special viosterol†	25.63	21.24	4.39	1,137	3.43	0.70	2.29	2.99	0.44	2.78	1.65	1.07	2.72	0.06
	57	6 Gm. special viosterol†	25.63	20.19	5.44	1,317	3.43	0.76	2.41	3.17	0.26	2.78	1.52	1.23	2.75	0.03
	58	Same dose of viosterol plus 36 cc. 10 per	25.63	21.81	3.82	1,901	3.43	0.85	2.17	3.02	0.41	2.78	1.75	1.20	2.95	—0.17
	59	cent hydrochloric acid	25.63	22.41	3.22	1,789	3.43	0.98	2.32	3.30	0.13	2.78	1.85	1.31	3.16	—0.38
	60	Same dose of viosterol only	25.63	23.86	1.77	1,745	3.43	0.90	1.91	2.90	0.53	2.78	1.86	0.95	2.81	—0.03
	61	Same dose of viosterol only	25.63	23.75	1.88	1,459	3.43	0.71	2.19	2.90	0.53	2.78	2.04	1.27	3.31	—0.53
	62	Same dose of viosterol plus 90 cc. 10 per	25.63	25.13	0.50	1,735	6.59	1.50	3.78	5.28	1.31	2.78	1.76	1.27	3.03	—0.25
	63	cent calcium chloride	25.63	24.88	0.75	2,034	6.59	1.63	4.25	5.88	0.71	2.78	1.73	1.55	3.28	—0.50
	64	Same dose of viosterol plus 90 cc. 10 per cent calcium chloride	25.63	26.50	—0.87	2,221	6.64	1.86	3.97	5.83	0.81	2.84	1.94	0.89	2.83	0.01

* Two day period. Observed results multiplied by 3/2.
† Ten times usual strength (2,500 D). Six grams represents 15 mg. of pure crystalline vitamin D, or 600,000 U. S. P. XI units of vitamin D.

The significant findings in regard to the calcium and phosphorus exchange during this first metabolism study may be summarized as follows: (1) high normal concentration of serum calcium, or slight hypercalcemia, (2) high fecal excretion of calcium, not significantly improved by the supplements used, (3) good retention of injected calcium, indicating no difficulty in utilizing calcium once it arrived in the blood stream, (4) constantly low concentration of serum phosphorus, (5) relatively low urinary and high fecal excretion of phosphorus, and (6) ability to absorb and retain satisfactorily phosphorus fed as di-sodium hydrogen phosphate.

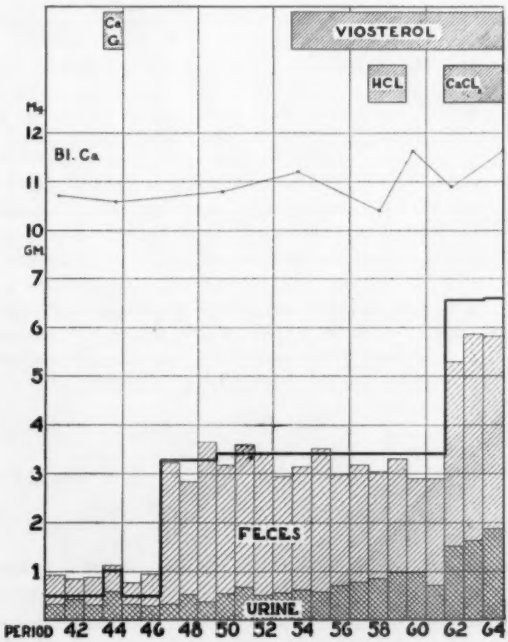

Fig. 3.—Calcium exchange and concentration of calcium in the serum during the second metabolism study of Z. K. after roentgen therapy was administered to the hypophysis. The heavy line represents the total intake, and each column represents the excretion of calcium during one period (three days).

Second Study.—After this first study was completed, the patient was given roentgen therapy to the pituitary gland and discharged. When he returned, two months later, further study of the calcium and phosphorus exchange was made in order to determine whether the roentgen therapy had caused any change in the metabolism of these elements and to test further the effects of certain supplements. The results of this second study appear in table 3 and in charts 3 and 4.

For six periods the patient was fed the same low calcium diet that was used during the first seven periods of the first study. The calcium and phosphorus exchange was essentially the same except for somewhat lower urinary excretion of calcium (the patient's weight was 20 Kg. less than at the beginning of the first study). During period 44 the same amount of calcium gluconate was injected as that given in period 18, in exactly the same manner. Owing to the low level of ingestion and excretion of calcium, the disposition of the injected calcium could be more accurately determined. On this occasion the results were exactly the same as those previously noted; the fecal excretion of calcium remained unchanged;

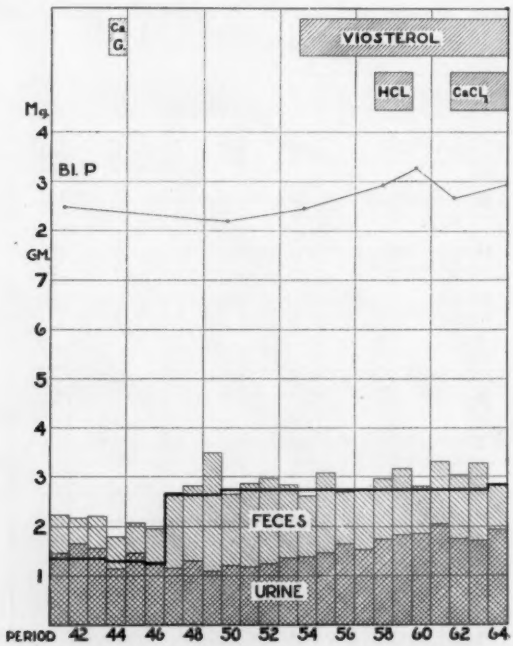

Fig. 4.—Phosphorus exchange and concentration of phosphorus in the serum during the second metabolism study of Z. K. after roentgen therapy was administered to the hypophysis. The heavy line represents the total intake, and each column represents the excretion of phosphorus during one period (three days).

the urinary excretion increased, and much of the injected calcium was retained, together with sufficient phosphorus for the formation of tribasic calcium phosphate. This is clearly shown in charts 3 and 4.

During periods 47, 48 and 49 the same high calcium, low calory diet that was used in the latter part of the first study was fed. The exchange of calcium and phosphorus during these periods was essentially the same as that found previously under these conditions. The concentration of calcium in the serum was slightly lower than that during the first study; the concentration of phosphorus was essentially the same. It is obvious, then, that the roentgen therapy had not altered the calcium and phosphorus metabolism in a recognizable way.

Further studies were then carried out. Up to that time the diet had always been undernourishing. In order to learn whether this low calory diet might affect the mineral metabolism, a diet with essentially the same calcium value but supplying the number of calories required for maintenance was fed throughout the remainder of the study. The concentration of calcium and phosphorus in the serum and the urinary excretion of these elements rose slightly. The balance remained essentially the same as when the low calory diet was fed. Beginning with period 54, the patient was fed 6 Gm. of a concentrated solution of viosterol,[13] supplying 600,000 U. S. P. XI units of vitamin D per period. After an initial slight increase, the fecal excretion of calcium decreased slightly; the urinary excretion increased, and the calcium balance was only slightly improved. This effect is essentially the same as that found by Bauer, Marble and Claflin [14] in normal persons. It is interesting to note that the concentration of calcium in the serum decreased and the concentration of phosphorus increased significantly during the administration of vitamin D in this large dosage.

Because an analysis of the gastric juice showed hypo-acidity, the effect of hydrochloric acid was studied. When hydrochloric acid was administered, the concentration of calcium in the serum rose sharply, the concentration of phosphorus rose less noticeably, the fecal excretion of calcium decreased slightly, the fecal excretion of phosphorus remained essentially unchanged and the urinary excretion of these elements was increased.

When calcium chloride was given, the absorption of calcium was better than at any time previously. The concentration of calcium in the serum was increased. The urinary excretion of calcium was doubled, so that, even though the balance was more positive than at any other time, the retention was not great. There was no appreciable change in the phosphorus metabolism.

It was planned to note the mineral metabolism after the cessation of administration of calcium chloride and later of viosterol, but owing to the necessary discharge of the patient these observations could not be made.

OBSERVATIONS ON A CONTROL SUBJECT

The interpretation of these findings presents several problems. Published studies of calcium and phosphorus exchange in normal adults are so few and meager that it was thought advisable to control this study by noting the response of a normal young adult to some of the diets and supplements administered to the patient.

Such a control study was conducted on a graduate student living his usual active life. The subject was 26 years old and weighed 64 Kg.; the calcium content of the serum was 11.1 mg. per hundred cubic centimeters and the phosphorus content 4.4 mg. The methods of study and of chemical analysis were exactly as described for the patient. The results are shown in table 4 and in charts 5 and 6.

For the first four periods, the control subject was fed a diet identical to that given the patient during periods 50 through 64 (containing 3.4 Gm. of calcium).

---

13. The viosterol was supplied by the Winthrop Chemical Company, Inc.

14. Bauer, W.; Marble, A., and Claflin, D.: Studies on the Mode of Action of Irradiated Ergosterol: I. Its Effect on the Calcium Phosphorus and Nitrogen Metabolism of Normal Individuals, J. Clin. Investigation **11**:1 (Jan.) 1932.

TABLE 4.—*Calcium and Phosphorus Exchange of Normal Control Subject*

Diet	Period	Medication	Nitrogen			Total Urinary Acid,	Calcium					Phosphorus				
			Intake, Gm.	Output, Gm.	Balance, Gm.	Cc. N/10 Acid	Intake, Gm.	Urine, Gm.	Feces, Gm.	Total Excretion, Gm.	Balance, Gm.	Intake, Gm.	Urine, Gm.	Feces, Gm.	Total Excretion, Gm.	Balance, Gm.
High calcium, 2,000 calories, calcium-phosphorus ratio 1.23	1	.....	25.63	34.02	—8.39	.....	3.40	0.26	2.77	3.03	0.37	2.91	2.60	1.02	3.62	—0.71
	2	.....	25.63	33.27	—7.64	.....	3.40	0.35	2.83	3.18	0.22	2.87	2.69	1.17	3.86	—0.99
	3	.....	25.63	31.45	—5.82	.....	3.40	0.30	2.08	2.38	1.02	2.76	2.28	0.67	2.95	—0.19
	4	.....	25.63	29.74	—4.11	.....	3.40	0.33	3.65	3.98	—0.58	2.66	2.45	1.32	3.77	—1.11
High calcium, 3,200 calories, calcium-phosphorus ratio 0.95	5	.....	34.0	35.73	—1.73	.....	3.55	0.29	2.67	2.96	0.59	3.80	2.47	1.45	3.92	—0.12
	6	.....	34.0	35.34	—1.34	.....	3.55	0.36	2.66	3.02	0.53	3.78	2.39	1.43	3.82	—0.04
	7	.....	34.0	36.89	—2.89	.....	3.55	0.41	2.86	3.27	0.28	3.87	2.47	1.46	3.93	—0.06
	8	Calcium hydrogen phosphate 14.3 Gm.....	34.5	34.43	0.07	.....	7.51	0.54	6.82	7.36	0.15	6.50	3.54	3.32	6.86	—0.36
	9	Calcium hydrogen phosphate 14.3 Gm.....	34.5	*	*	.....	7.51	*	7.13	*	*	6.50	*	3.31	*	*
	10	Calcium hydrogen phosphate 14.3 Gm.....	34.5	34.00	0.50	.....	7.51	0.43	6.54	6.97	0.54	6.50	3.26	2.43	5.69	0.81
	11	Calcium hydrogen phosphate 14.3 Gm.....	34.5	38.00	—3.50	.....	7.51	0.50	6.46	6.96	0.55	6.70	3.66	2.04	5.70	1.00
	12	.....	34.0	33.04	0.96	1,973	3.55	0.33	4.42	4.75	—1.20	3.71	2.35	2.33	4.68	—0.97
	13	36 cc. 10 per cent hydrochloric acid.....	34.0	35.00	—1.00	2,285	3.55	0.37	3.00	3.37	0.18	3.77	2.52	1.70	4.22	—0.45
	14	36 cc. 10 per cent hydrochloric acid.....	34.0	33.40	0.60	2,410	3.55	0.41	2.47	2.88	0.67	3.71	2.51	1.13	3.64	0.07
	15	.....	34.0	34.66	—0.66	1,804	3.55	0.40	3.19	3.59	—0.04	3.75	2.64	1.58	4.18	—0.43
	16	90 cc. 10 per cent calcium chloride.....	34.0	35.31	—1.31	2,122	6.71	0.81	5.70	6.51	0.20	3.78	2.19	1.54	3.73	0.05
	17	90 cc. 10 per cent calcium chloride.....	34.0	35.36	—1.36	2,615	6.71	0.71	4.85	5.56	1.15	3.78	2.15	1.33	3.48	0.30
	18	.....	34.0	35.85	—1.85	2,438	3.55	0.44	4.18	4.62	—1.07	3.82	2.69	1.71	4.40	—0.58
	19	.....	34.0	31.20	2.80	1,897	3.55	0.46	3.26	3.72	—0.17	3.71	2.29	1.63	3.92	—0.21

* Part of the urine was lost.

The caloric value of the diet was considerably below that required to keep him in energy balance. During that time the urinary excretion of calcium was slightly less than that of Z. K. while he was on this diet but was equal to the urinary excretion of Z. K. when he was fed an undernourishing diet with a similar calcium content. The fecal excretion of calcium was essentially the same as that of the patient when fed this diet. The calcium balance was slightly positive.

The phosphorus exchange was decidedly different from that observed in Z. K. The urinary excretion of phosphorus was more than twice as great as the fecal secretion, which is the usual partition of this element in the excreta of normal persons. This is in contrast to the patient's excretion of phosphorus, most

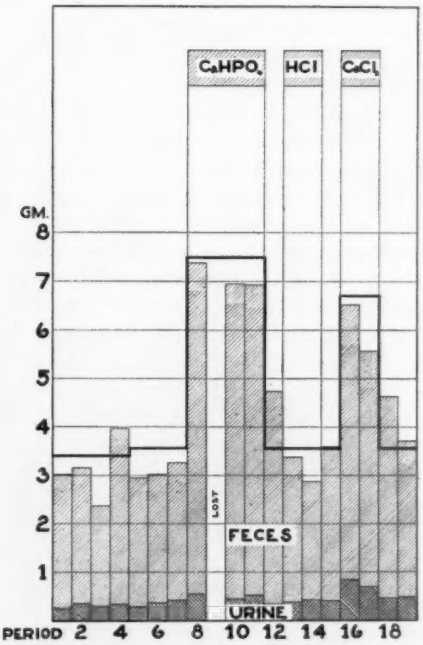

Fig. 5.—Calcium exchange of the normal control subject. The heavy line represents the intake, and each column represents the excretion of calcium during one period (three days).

of which was in the feces. Moreover, the excretion of phosphorus in the urine of the control subject was twice as great as that of the patient when he was fed the same diet.

Because this diet was undernourishing for the control subject, beginning with period 5 and continuing throughout the remainder of the study, a diet was fed which supplied essentially the same amount of calcium with the number of calories required for maintenance. The calcium and phosphorus exchange was essentially unchanged.

When calcium hydrogen phosphate was fed in amounts equivalent to those fed the patient, the urinary excretion of calcium rose significantly (distinctly different

from the patient's response); the fecal excretion and the calcium balance, however, were similar to those of the patient. Likewise, the urinary excretion of phosphorus increased decidedly; the fecal excretion was less than that of the patient, and the phosphorus balance was positive. These observations indicate that the control subject absorbed more of the calcium hydrogen phosphate than did the patient.

When hydrochloric acid was fed to the control subject in an amount equal to that fed to Z. K., the acidity of the urine and the urinary excretion of calcium were increased by much smaller amounts than in the patient. The phosphorus exchange was not affected.

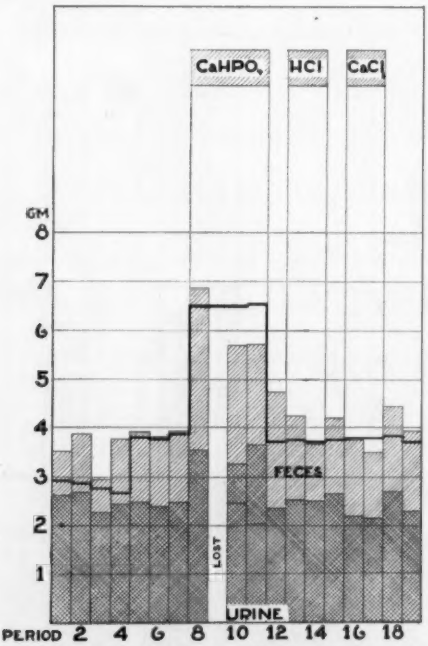

Fig. 6.—Phosphorus exchange of the normal control subject. The heavy line represents the intake, and each column represents the excretion of phosphorus during one period (three days).

Calcium chloride fed to the control subject in exactly the same way as it was given to the patient caused only a slight rise in the acidity of the urine and a smaller increase in urinary excretion of calcium than was found for the patient. The urinary excretion of phosphorus decreased slightly, and the phosphorus balance became slightly positive.

COMMENT

When the mineral exchange of the patient is compared with that of the control subject, it is noted that the calcium metabolism of the patient differed in the following ways: The urinary excretion of calcium

at times was slightly greater; it did not increase when calcium hydrogen phosphate was administered, but there was a greater increase when hydrochloric acid and calcium chloride were taken. Even more striking differences are noted in the phosphorus metabolism. The concentration of phosphorus in the patient's serum was constantly low; the urinary excretion of phosphorus was small, and there was a reversal of the normal partition of phosphorus in the urine and feces.

When the mineral metabolism of our patient is compared with that existing in a state of hyperparathyroidism, several noteworthy differences are evident. Bauer [15] pointed out that hyperparathyroidism is characterized by (1) an elevated concentration of serum calcium, (2) a decreased concentration of serum phosphorus and (3) increased urinary excretion of both calcium and phosphorus. Albright [16] showed that the primary effect of the parathyroid hormone, however, is to increase the urinary excretion of phosphorus by lowering the renal threshold for the excretion of this element. This same investigator [17] also pointed out that patients with hyperparathyroidism have no difficulty in absorbing calcium and that if there is a liberal ingestion of this element enough calcium is absorbed so that the calcium balance becomes positive despite the resultant increase in urinary excretion.

With these facts in mind, it is at once evident that the mineral metabolism in our patient is not characteristic of hyperparathyroidism. In keeping with this, the parathyroid bodies showed nothing histologically to suggest hyperactivity: they were not enlarged; no zones of proliferation or adenomas were present; they were grossly infiltrated with fat.

It is noteworthy that in the reports of verified cases of pituitary basophilism (table 1) there is no instance of hypercalcemia. In all cases in which skeletal decalcification was present concentration of serum phosphorus was low.

One of the most interesting features of the mineral metabolism in our patient was the failure to absorb more than small amounts of calcium even though there was great need for it. Bauer [18] has shown that

15. Bauer, W.: Hyperparathyroidism: A Distinct Disease Entity, J. Bone & Joint Surg. **15**:135 (Jan.) 1933.

16. Albright, F.; Bauer, W.; Ropes, M., and Aub, J. C.: Studies of Calcium and Phosphorus Metabolism: IV. The Effect of the Parathyroid Hormone, J. Clin. Investigation **7**:139 (April) 1929.

17. Albright, F.; Bauer, W.; Claflin, D., and Cockrill, J. R.: Studies in Parathyroid Physiology: III. The Effect of Phosphate Ingestion in Clinical Hyperparathyroidism, J. Clin. Investigation **11**:411 (March) 1932.

18. Bauer, W., and Marble, A.: Studies on the Mode of Action of Irradiated Ergosterol: II. Its Effect on the Calcium and Phosphorus Metabolism of Individuals with Calcium Deficiency Diseases, J. Clin. Investigation **11**:21 (Jan.) 1932.

certain patients with calcium deficiency diseases can be caused to absorb and retain large amounts of calcium when a potent preparation of vitamin D is administered. This supplement, even when fed in huge doses to our patient, caused little, if any, benefit. The unusual mineral metabolism and skeletal decalcification cannot be due, therefore, to vitamin D deficiency.

The persistence in our patient of epiphyses which normally should have disappeared certainly indicates that some abnormality of the calcium and phosphorus metabolism other than simple osteoporosis exists.

CONCLUSIONS

The calcium and phosphorus exchange in a case of verified pituitary basophilism is reported. The findings considered most noteworthy are: (1) a low concentration of serum phosphorus, (2) a low urinary and a high fecal excretion of phosphorus, (3) failure to absorb sufficient calcium and phosphorus to allow retention of appreciable amounts of these elements, even though there was great need for calcium phosphate in the skeleton, (4) failure of vitamin D and other supplements to increase appreciably the absorption and retention of calcium and (5) good utilization of calcium injected intravenously.

This patient's metabolism of calcium and of phosphorus is not characteristic of hyperparathyroidism.

A complete understanding of the abnormalities of the mineral metabolism in cases of pituitary basophilism must await further studies.

THE OBESITY AND ENERGY EXCHANGE IN A VERIFIED CASE OF PITUITARY BASOPHILISM

R. H. FREYBERG, M.D.
AND
L. H. NEWBURGH, M.D.
ANN ARBOR, MICH.

Obesity is frequently observed in patients who have lesions of the hypophysis. The adiposity associated with Fröhlich's syndrome is well known. Cushing [1] recently described a clinical syndrome resulting from basophil adenoma of the pituitary gland. One of the features of this syndrome is adiposity, which is said to be confined characteristically to the face, neck, thorax and abdomen, sparing the extremities. The abdomen is usually protuberant and often pendulous.

The feeling is prevalent that the obesity associated with dyspituitarism results from some unusual metabolic disturbance, which in a mysterious way causes an increased synthesis and deposition of body fat. The significance of hypercholesteremia, commonly present in cases of pituitary basophilism, has been variously interpreted. Kraus [2] suggested that a disturbance of fat metabolism with an associated hypercholesteremia may be the fundamental abnormality in Cushing's disease and that as a result of this metabolic disturbance lesions develop in the adenohypophysis (excess basophilia or basophil adenoma) and in the adrenal bodies (cortical hyperplasia or adenoma) which in turn produce the striking clinical manifestations of this syndrome.

In a previous paper [3] we reported a case of Cushing's disease showing the classic clinical syndrome, in which the diagnosis was verified by the finding of a basophil adenoma of the adenohypophysis at post-

From the Department of Internal Medicine, Medical School, University of Michigan.

1. Cushing, H.: The Basophil Adenomas of the Pituitary Body and Their Clinical Manifestations (Pituitary Basophilism), Bull. Johns Hopkins Hosp. **50**:137 (March) 1932.

2. Kraus, E. J.: Relation of Chromophil Cells of the Hypophysis to Carbohydrate, Fat and Cholesterol Metabolism; Study of Cushing's Pituitary Basophilism, Med. Klin. **29**:449 (March) 1933.

3. Freyberg, R. H.; Barker, P. S.; Newburgh, L. H., and Coller, F. A.: Pituitary Basophilism (Cushing's Syndrome): Report of a Verified Case, with a Discussion of the Differential Diagnosis and Treatment, Arch. Int. Med., this issue, p. 187.

mortem examination. The patient was under observation for the greater part of a year, during which time various metabolic studies were made. The calcium and phosphorus exchange in this patient is described in a separate paper.[4] The purpose of this communication is to report the results of a study of the energy exchange in this patient.

In normal persons, when the outflow of energy exceeds the inflow, the difference is furnished by the oxidation of body tissues according to well established principles. After the first few days on a reduction diet, the caloric deficit is met by the combustion of body fat and by a small amount of body protein if the diet is low in protein. The amount of body protein burned can be readily determined if the amount of dietary and excretory nitrogen is known. The total caloric deficit minus that portion furnished by the combustion of body protein is met by the combustion of body fat. Knowing the calorific value of the body protein and fat burned, one can determine the weight of each of these materials destroyed. This weight, together with the weight of the water physically attached to the tissues, which is liberated when the tissues are burned, represents the total loss of weight of the subject.

OBSERVATIONS ON THE PATIENT

The inflow of energy was kept constant and small in our patient by a diet supplying only 890 calories daily. The composition of the diet was exactly the same day after day. The outflow of energy was determined for nine successive twenty-four hour periods by the method described by Newburgh and his associates.[5] Assuming that the energy expenditure continued at a rate equal to the average for the nine days during which it was measured, it was predicted that at the end of fifty-four days (the length of time the patient was fed this same diet without interruption) the weight should be reduced by 8,376 Gm. The actual record of the weight showed the loss to be 8,398 Gm., or 22 Gm. more than the predicted loss based on normal energy exchange.

Figure 1 shows graphically the actual and predicted weights during this period of study. It is seen that the actual loss of weight varies only slightly from the straight line of predicted loss of weight. This exceptionally good agreement exists because not only was the caloric intake constant but the mineral and fluid intake was identical day after day, and the activity of the patient was essentially the same each day. Consequently, the error experienced was less than 0.3 per cent.

This excellent agreement between the actual weight and the weight predicted on the basis of normal disposition of energy-supplying materials indicates certainly that the energy exchange in this patient during the period of weight reduction was entirely normal. There was, therefore, no unusual metabolic feature acting

4. Freyberg, R. H., and Grant, R. L.: Calcium and Phosphorus Metabolism in a Verified Case of Pituitary Basophilism, Arch. Int. Med., this issue, p. 213.

5. Newburgh, L. H.; Wiley, F. H., and Lashmet, F. H.: A Method for the Determination of Heat Production over Long Periods of Time, J. Clin. Investigation **10**:703 (Oct.) 1931.

as the cause of obesity. He became obese because the inflow of energy exceeded the expenditure of energy; the excess energy being stored in the body in the form of fat.

The appearance of this patient at the time of admission gave the impression that the adiposity was largely confined to the head, neck and trunk. After the patient had lost 22.5 Kg. of adipose tissue, the unusually prominent chest and abdomen had been little altered and had not diminished in size any more than had the extremities (figs. 2 and 3). Hence the disproportionate enlargement of the trunk could not have been due simply to adiposity. A lateral roentgenogram of the chest shows the actual reason for the abnormal configuration (fig. 4). The thinness of the vertebral bodies allowed a shortening of the spine and kyphosis. As a result, the thorax had a greatly increased anteroposterior diameter.

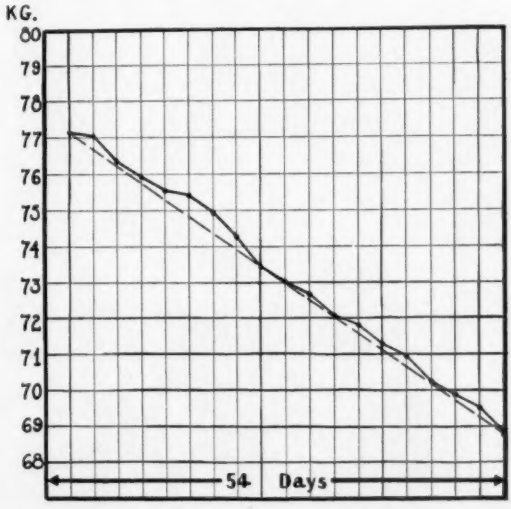

Fig. 1.—The predicted and actual weight curves over a fifty-four day period of undernutrition. The broken line represents the predicted weight, and the solid line indicates the actual weight. The predicted total loss was 8,376 Gm., and the actual loss was 8,398 Gm.

Another interesting physical finding in this patient was the apparent absence of scrotum and penis noted on admission. In this respect, the appearance of the patient closely resembled that characteristic of Fröhlich's syndrome. When the patient's weight was reduced, there was seen to be a definite but small penis and small gonads contained in a normal-appearing scrotum (fig. 5). The apparent absence of external genitalia in this case is seen to be due chiefly to the fact that they were hidden in the abundant pubic fat.

The basal metabolic rate was —2 per cent (a normal value) at the beginning of the study. After three months on the reduction diet, the rate of basal metabolism decreased to —24 per cent, the usual response to undernutrition.

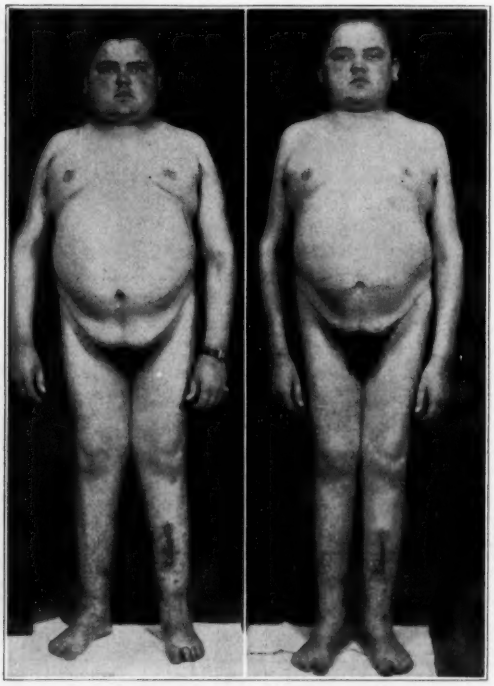

Fig. 2.—Front view of the patient before and after he lost 22.5 Kg. in response to undernutrition.

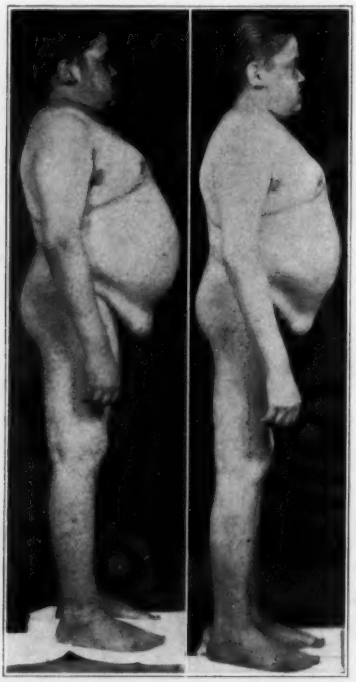

Fig. 3.—Lateral view of the patient before and after he lost 22.5 Kg. in response to undernutrition.

Hypercholesteremia did not exist in our patient. The concentration of cholesterol in whole blood was 165 mg. per hundred cubic centimeters.[6] Duplicate analyses of a mixture of equal portions of cerebrum and cerebellum removed at autopsy

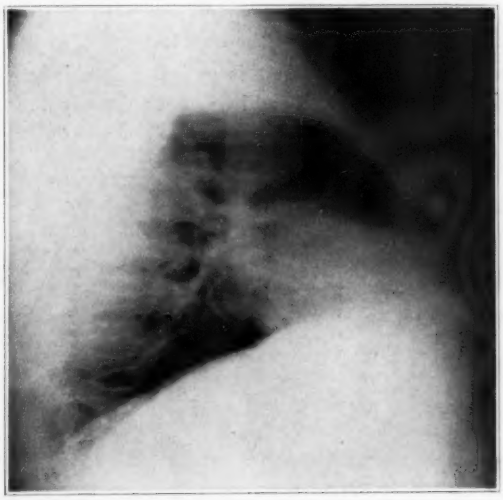

Fig. 4.—A lateral roentgenogram of the chest, showing the increased antero-posterior diameter, the horizontal course of the ribs, the high diaphragm and the transverse position of the heart.

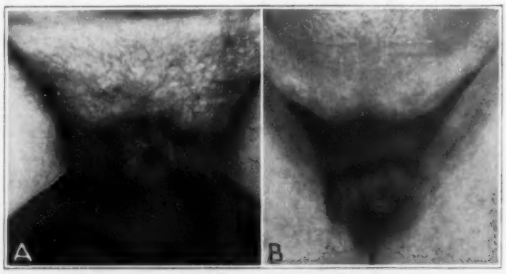

Fig. 5.—The genitalia, *A*, hidden in pubic fat at the time of admission and, *B*, plainly visible after reduction of weight.

showed 2.34 gm. of cholesterol per hundred grams of tissue. This is a normal value.

6. All determinations of cholesterol were made by a modification of the digitonin precipitation method of Windaus.

CONCLUSIONS

In a patient with verified pituitary basophilism undernutrition caused loss of weight exactly as predicted for a normal person, thus demonstrating a normal energy exchange and the absence of any unusual metabolic feature as the cause of the obesity.

The unusual configuration in this patient was chiefly the result of an underlying skeletal deformity and was not primarily due to adiposity.

CHRONIC PULMONARY INFECTION DUE TO THE FRIEDLÄNDER BACILLUS

FURTHER OBSERVATIONS

LEON H. COLLINS JR., M.D.
PHILADELPHIA

In previous publications [1] from this hospital, my associates and I described the clinical and roentgenologic features of three cases of pneumonia with recovery and expressed the belief that the organism responsible for the production of the pulmonary lesion was the Friedländer bacillus (Bacillus mucosus-capsulatus). In two of these cases the onset suggested bronchopneumonia; in one, lobar pneumonia. The temperature fell by lysis in all cases, and in all the total leukocyte count tended to be lower than that seen in the usual case of pneumococcic lobar pneumonia. The outstanding finding on physical examination was the extreme indolence of the lesion in the lung. We expressed the belief that there are characteristic roentgen signs which serve to differentiate this condition from other pulmonary infections. Several months after the acute infection had subsided, evidence of pathologic change in the lung could still be demonstrated both by physical and by roentgen examination. On the basis of the studies reported at that time, we expressed the belief that there is a chronic form of pulmonary disease caused by B. mucosus-capsulatus. We further expressed the belief that in many respects the chronic form of this disease simulated chronic pulmonary tuberculosis and therefore that in cases of suspected tuberculosis in which the sputum had never shown Bacillus tuberculosis it should be examined for B. mucosus-capsulatus.

My purpose in the present paper is twofold: first, to present follow-up data on these three original cases, and, second, to record observations made by my associates and me on a fourth nonfatal case in which we succeeded in isolating the Friedländer bacillus in a culture of the blood during the height of the pneumonia.

From the medical clinic, Hospital of the University of Pennsylvania.

1. (*a*) Stengel, A.; Kornblum, K., and Collins, L. H., Jr.: Friedländer's Pneumonia; Clinical and Roentgenological Study of Cases with Special Reference to a Chronic Form Simulating Pulmonary Tuberculosis, Tr. A. Am. Physicians **43**:326, 1928. (*b*) Kornblum, K.: The Roentgen Ray Diagnosis of Pulmonary Infections with Friedländer's Bacillus, Am. J. Roentgenol. **19**:513, 1928. (*c*) Collins, L. H., Jr., and Kornblum, K.: Chronic Pulmonary Infection Due to Friedländer's Bacillus: A Clinical and Roentgenologic Study, Arch. Int. Med. **43**:351 (March) 1929.

OBSERVATIONS ON CASES

Of the original cases, we have the most complete data on case 1.

CASE 1.—J. A. is now 58 years of age. He was admitted to the hospital in 1927, in a diabetic coma, with an illness that already has been described.[1c] In the intervening years he has attended the outpatient department of the hospital for the treatment of his diabetes, and both his diabetic and his pulmonary status have been followed. During these years he has suffered neither from frequent colds nor from additional attacks of pneumonia. At the time of writing he has no pulmonary symptoms. Physical examination of the chest reveals moderate impairment in the percussion note over the right side of the chest anteriorly. Over the lower half of the right lung anteriorly and in the right axilla many fine râles are heard. At the base of the right lung, posteriorly the expiratory phase of respiration is prolonged, but no râles are heard.

The roentgen studies of this patient, extending from 1927 to 1934, have been of particular interest. In a previous paper[1c] we included five roentgenograms of this patient's lungs, showing (1) the primary stage of bronchopneumonia, (2) the pseudolobar stage, (3) the stage of multiple abscess and cavity formation, (4) the stage of fibrosis, revealing the appearance of the lungs at the time of the patient's discharge from the hospital and (5) the chronic stage, approximately ten and one-half months after the onset of the acute pneumonia.

Figure 1 *A* shows the chest on March 10, 1933. There had been marked improvement in the appearance of the chest since the examination in 1927. There still remained, however, a definite diffuse fibrosis throughout the right lung. Figure 1 *B* shows the chest on Sept. 20, 1933. At that time the right lung was the seat of fibrous strands, the crossing of which simulated thin-walled cavities. The right dome of the diaphragm was elevated and wavy, largely in the anterior portion of the chest, indicating that the greater part of the pathologic process was in the upper and middle lobes. Figure 1 *C*, taken on June 19, 1934, showed that the condition of the chest was essentially the same as on Sept. 20, 1933. The right lung was the seat of many fibrous strands. There was no evidence of cavitation. There was marked peaking of the dome of the diaphragm on the right side. In summary, the lungs of this patient showed chronic changes by clinical and roentgenologic examination which we believe are attributable to acute pneumonia produced by B. mucosus-capsulatus in 1927.

CASE 2.—M. P., a thin white woman, was admitted to the hospital on Feb. 9, 1927, and was discharged on April 6, 1927. At that time she was 50 years of age. The last contact that we had with this patient was six and one-half months after her discharge from the hospital. At that time, however, physical examination still revealed signs at the base of the left lung and roentgen examination[2] showed a cavity remaining in the region of the old abscess with fibrosis in the base of the left lung.

Because of the death of the original referring physician and of the patient's relatives, we have been able only recently to secure follow-up information concerning this patient. Through the kindness of the Mount Sinai Hospital of Philadelphia we obtained the following data in a letter of July 10, 1934: "M. P., aged 51, was admitted to this hospital on Feb. 16, 1929, and died on Feb. 17, 1929, with a final diagnosis of thrombosis involving the vessels of the left lower extremity and probably also the left iliac vein following sepsis (confirmed by postmortem examination).

2. Collins and Kornblum,[1c] fig. 11.

"The patient was admitted on the evening of Feb. 16, 1929. Three weeks before admission an acute sore throat developed, which the family said was diagnosed by a physician as diphtheria and for which she received antitoxin. Two weeks before admission the patient became irrational, and because she became more toxic and appeared moribund, another physician was called, who sent her to this hospital.

"Examination revealed a white woman, extremely toxic, very irrational and markedly cyanotic; the left pupil was smaller than the right and reacted sluggishly to light; the throat was slightly congested, but no membrane was visible;

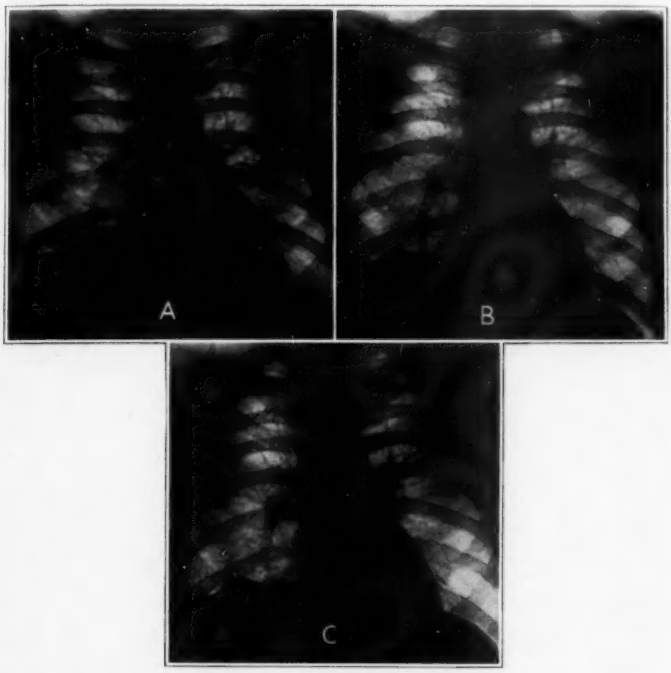

Fig. 1 (case 1).—*A*, roentgenogram taken on March 10, 1933, showing a marked improvement in the appearance of the chest since the last examination in 1927. There still remained, however, a definite fibrosis throughout the right lung. *B*, roentgenogram taken on Sept. 20, 1933. The right lung was the seat of fibrous strands, the crossing of which simulated thin-walled cavities. *C*, roentgenogram taken on June 19, 1934. The right lung was the seat of many fibrous strands. No evidence of cavitation was present. Marked peaking of the dome of the diaphragm was present on the right side.

the lungs were clear; the heart was very rapid; the rhythm was irregular and the first and second sounds approximated each other; the blood pressure was 90 systolic and 50 diastolic; the abdomen was normal except for edema and tenderness of the left lower quadrant; the entire left lower extremity was

edematous and was about one and one-half times the diameter of the right; there was a beginning area of gangrene of the left foot; the dorsalis pedis artery of the left foot was not palpable; on the right side the pulse was good. Examination of the pelvis failed to reveal any palpable mass that would produce pressure on the return circulation.

"Laboratory studies on admission revealed a normal hemoglobin content and red cell count; 18,000 leukocytes per cubic millimeter, with 78 per cent polymorphonuclears; a highly concentrated urine, with an occasional white cell and loaded with hyaline and granular casts; 33 mg. of urea nitrogen per hundred cubic centimeters; a normal sugar content of the blood; normal serologic reactions, and a spinal fluid cell count of 18 leukocytes per cubic millimeter.

"The temperature on admission was 103 F., the pulse rate was 150 and the respiratory rate was 40. The patient died eighteen hours after admission, with a temperature of 107 F. and a pulse too rapid to count."

The following are excerpts from the autopsy notes: "Acute splenitis was present, and there was cloudy swelling of the liver. The vena cava inferior and the right iliac vein were empty. The left iliac vein was filled with thrombus. Histologic examination of other organs revealed evidence of acute passive congestion and cloudy swelling. A culture of blood from the heart showed no growth after forty-eight hours. The left lung contained no adhesions. The pleura presented no abnormalities. No consolidations were felt. The cut surface presented a great deal of chronic passive congestion. The right lung showed the same changes."

From the standpoint of our particular interest in the pathologic changes in this patient, it is unfortunate that neither the paraffin blocks nor the lungs were saved. Also the autopsy notes do not indicate the portion of the lung from which tissue was removed for histologic examination. Consequently, we are left without information concerning the eventual fate of the abscess in the lower lobe of the left lung.

CASE 3.—T. M., a well developed Negro aged 43, was admitted to the hospital on March 5, 1927, with the history and symptoms of acute lobar pneumonia. He was discharged on May 5, 1927, to spend a few weeks at a home for convalescents before returning to work as a laborer. This man belonged to the floating Negro population that comprises a portion of the southern section of this city. A painstaking search, both in Philadelphia and in Virginia, whence he originally came, has failed to locate him.

In a former paper,[3] we stated that to the best of our knowledge, in all cases of pneumonia due to Friedländer's bacillus in which the organism has been recovered from the circulating blood the condition has ended fatally. It is true that in our cases reported at that time blood cultures remained sterile, but the repeated recovery of this organism in profuse growth from the sputum, together with the clinical and roentgenologic features of these cases, we felt, justified the conclusion that the pulmonary lesions had been produced by the Friedländer bacillus.

With the passage of time we have retained confidence in this conclusion because of data obtained in our fourth case, in which B. mucosus-capsulatus was recovered from the blood stream during the acute stage of the pneumonia.

3. Collins and Kornblum,[1c] p. 360.

CASE 4.—J. J., a well developed Italian laborer, aged 63, was admitted to the hospital on Dec. 18, 1932, and was discharged on Feb. 16, 1933. His chief complaint on admission was pain in the right side of the chest. Apparently he had been well until four days before admission, when, without any history of exposure or trauma, he arose in the morning and had a chill which lasted about an hour.

During that time he felt alternately hot and cold. He spent the remainder of that day in bed, and when he awoke on the following day he had severe pain in the entire right side of the chest, anteriorly and posteriorly. Also there was great difficulty in breathing, with much coughing productive of large amounts of bloody sputum. At that time his physician said that his lungs were congested. During the two following days his general condition became steadily worse, and when delirium supervened his physician decided to send him to the hospital at once. We calculated that he was admitted on the fifth day of his illness.

This patient had never had pneumonia previously and apparently was not susceptible to other forms of disease of the respiratory tract. The past medical and the family history were irrelevant. He had always been a heavy drinker of wine.

At the time of his admission to the hospital the temperature was 101.8 F., the pulse rate 120 and the respiratory rate 40. The blood pressure was 110 systolic and 60 diastolic. At that time the patient did not appear particularly dyspneic, though there was distinct cyanosis of the cheeks, ears and lips. He did not appear to have pain in the chest. The chest was emphysematous, with a markedly obtuse subcostal angle. Expansion was fair, being slightly restricted on the right side. There was marked dulness to percussion, both anteriorly and posteriorly. The percussion note over the entire left lung seemed hyperresonant. Over the upper lobe of the right lung the breath sounds were tubular in quality, and over the anterior aspect of this lobe an occasional crackling râle was heard. At the base of the right lung posteriorly there were heard many fine crackling râles. The tentative diagnosis was pneumonia of the upper lobe of the right lung with possible involvement of the lower lobe.

On Dec. 19, 1932, the day following admission, the leukocytes numbered 12,800, of which 85 per cent were polymorphonuclears. Abdominal distention was marked. Cyanosis of the lips and nail beds was slight. The patient appeared drowsy at this time and remained so for several days thereafter. The abdominal distention was controlled by enemas and by repeated doses of physostigmine.

On December 2 physical signs of consolidation of the upper lobe of the right lung were still definite. It was concluded after physical examination that the middle and lower lobes were not involved. On December 22 the leukocyte count was 18,700, with 91 per cent polymorphonuclear neutrophils, 10 per cent being filamented forms and 81 per cent nonfilamented forms, 6 per cent lymphocytes and 3 per cent mononuclears. The Wassermann reaction of the blood was negative.

At that time there was only a moderate amount of cough, productive of grossly blood-tinged sputum. Culture of this sputum showed B. mucosus-capsulatus (Friedländer) in large numbers as the predominant organism. A blood culture taken on December 19 showed a pure culture of B. mucosus-capsulatus. As far as could be determined bacteriologically, the organisms found in the sputum and those isolated from the blood were identical.

Roentgenograms of the chest made by Dr. E. P. Pendergrass on December 23 (fig. 2*A*) were interpreted as follows: "Lobar pneumonia is present in the

upper lobe of the right lung. There is consolidation of this lobe, possibly beginning in the lower lobe, as the dome of the diaphragm is elevated posteriorly, having the appearance of being perfectly flat with a fluid level. I think, however, that this is due to a lack of aeration in the lower lobe."

A second blood culture, taken three days after the first one, was sterile. The roentgenogram of the chest taken on Dec. 27, 1932 (fig. 2 *B*), was interpreted by Dr. Pendergrass as follows: "Friedländer's pneumonia is present. There is resolving pneumonia in the upper lobe of the right lung. The irregular rarefactions suggest the formation of cavities." During these days the patient remained in

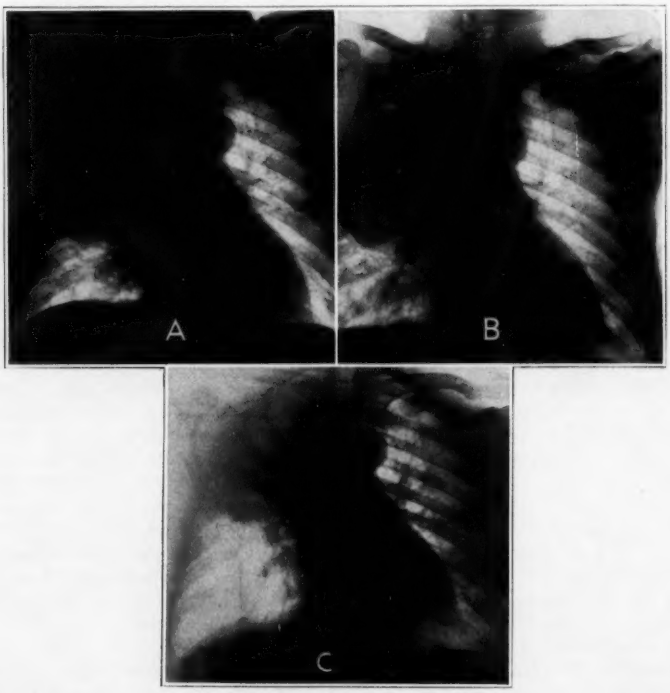

Fig. 2 (case 4).—*A*, roentgenogram taken on Dec. 23, 1932, showing consolidation of the right upper lobe. *B*, roentgenogram showing resolving pneumonia in the upper lobe of the right lung on Dec. 27, 1932. The irregular rarefaction suggests the formation of cavities. *C*, on Jan. 14, 1933, the lesion involving the right upper lobe was smaller. Multiple abscess cavities were present with fluid levels.

his drowsy state. There was a slight increase in the amount of cough. The type of sputum remained as it had been on admission, but the amount was smaller.

By December 30 the patient appeared much brighter mentally. The percussion note over the upper lobe of the right lung was less dull. Roentgenographic examination on Jan. 5, 1933, was reported as follows: "The diagnosis is Fried-

länder's pneumonia. The area of cavitation found in the previous examination is not as evident at this examination as previously. There is still involvement of the entire upper lobe of the right lung, but one obtains the impression that there has been some improvement." On January 10 the entire lobe still remained dull to percussion, both anteriorly and posteriorly. After coughing, cavernous breathing was distinctly heard anteriorly, associated with moist râles and whispering pectoriloquy. Culture of the sputum on January 14 still showed B. mucosus-capsulatus in moderate numbers. On January 14 (fig. 2*C*) Dr. Pendergrass reported: "The lesion involving the upper lobe of the right lung is smaller than at the previous examination. There are multiple abscess cavities present with fluid levels. The homogeneous density is probably due to the fact that the lesion extends outward and has caused a slight pleural reaction."

On January 23 the temperature had not risen above 99 F. for five days. The patient was becoming restless and declared that he was able to get up and go home. However, at that time there were still definite limitation in respiratory excursion and dulness to percussion over the entire upper lobe of the right lung. Auscultation revealed bronchial breath sounds. The red cell sedimentation rate on January 25 was markedly accelerated. Culture of the sputum on January 24, showed three colonies of B. mucosus-capsulatus, a moderate growth of green streptococci and a few organisms of the Micrococcus catarrhalis type. On January 27 (fig. 3*A*) Dr. Pendergrass' roentgen observations were: "The diagnosis is Friedländer's pneumonia. The lesion has improved slightly since the last examination. There are still multiple fluid levels in the upper lobe of the right lung. Surrounding these areas there is a homogeneous density, probably due to an atelectatic lung."

The patient was first allowed out of bed on January 24. Although his strength returned rather rapidly, the clinical and roentgenologic signs over the upper lobe of the right lung remained virtually unchanged. The sedimentation curve obtained on January 25 and that obtained on February 15 were almost superimposable. However, in spite of these facts, it was deemed safe to discharge the patient on February 16.

Treatment during this attack of pneumonia consisted entirely of supportive and symptomatic measures. No form of specific treatment was used. Resort was not made even to postural drainage.

After discharge the patient did not return to work. He felt well except for shortness of breath on the slightest exertion. Some edema of the ankles had been noted, which would disappear by the following morning. There was a small amount of sputum, which was never blood tinged.

The patient was readmitted to the hospital on May 8, particularly for a survey of the pulmonary lesion. The temperature and the pulse and respiratory rates were normal. The physical signs in the chest were very much as they had been three months previously. Over the upper lobe of the right lung there were limitation in expansion, dulness to percussion and cavernous breath sounds, with bronchophony and whispering pectoriloquy. Examination of the blood at that time showed 5,600,000 red cells, 7,000 white cells and 108 per cent hemoglobin (17.9 Gm.) per hundred cubic centimeters. The differential count showed 67 per cent polymorphonuclear neutrophils, 27 per cent lymphocytes, 5 per cent large mononuclears and 1 per cent eosinophils. Of the neutrophils, 36 per cent were of the filament form and 31 per cent were nonfilamented. A roentgenogram of the chest made on May 9 (fig. 3*B*) was interpreted as follows: "Chronic infection with Friedländer's bacillus is present, involving the upper lobe of the right lung. There has been considerable improvement in the appearance of the chest since

the last examination. There remains, however, considerable fibrosis involving the upper lobe of the right lung, with evidence of cavitation. There is also considerable thickening of the pleura at the extreme apex. The trachea and heart are still definitely drawn to the right." Examination of the sputum did not show B. mucosus-capsulatus.

On Nov. 8, 1934, the patient was again admitted to the hospital, complaining of cough and shortness of breath. However, there was no sputum. There was no pain over any portion of the chest. The temperature was 98 F., the pulse rate 66 and the respiratory rate 20. The blood pressure was 166 systolic and 88 diastolic. There was no cyanosis. The trachea was freely movable but was distinctly displaced to the right. There were still definite physical signs of involvement over the upper lobe of the right lung, consisting of a slight decrease in expiratory excursion and an increase in tactile fremitus, with distinct impairment in the percussion note. The breath sounds were bronchial in character. Egophony and whispering pectoriloquy were present in the apex of the right axilla. After the patient coughed, an occasional râle could be heard. The remainder of the chest was clear on physical examination.

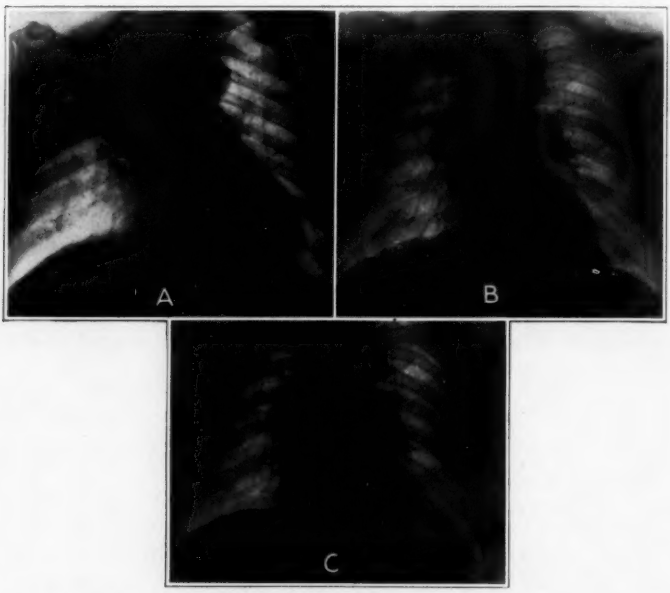

Fig. 3 (case 4).—*A*, roentgenogram taken on Jan. 27, 1933, showing slight improvement. There were still multiple fluid levels in the upper lobe of the right lung. *B*, roentgenogram taken on May 9, 1933, showing considerable improvement. There still remained, however, considerable fibrosis involving the upper lobe of the right lung, with evidence of cavitation. The trachea and heart were definitely drawn to the right. *C*, On Nov. 9, 1934, there were multiple annular shadows which simulated cavities having thin walls. There was some thickening of the apical pleura, with displacement of the trachea toward the right.

Hematologic examination on Nov. 11, 1934, showed 4,500,000 red cells, 7,000 leukocytes and 85 per cent hemoglobin; 68 per cent of the leukocytes were polymorphonuclears.

The erythrocyte sedimentation rate was much slower than it had been on the two previous occasions. Because there was no sputum, material from the throat was examined by smear and culture. The smear showed an occasional polymorphonuclear leukocyte, gram-positive cocci and short chains and occasional gram-negative rod forms. Culture showed a predominance of pneumococci, a moderate number of nonhemolytic streptococci, an occasional organism identified as Micrococcus catarrhalis and an occasional hemolytic streptococcus. No organisms of the mucosus group were seen.

The report of examination of the chest on Nov. 9, 1934 (fig. 3*C*), by Dr. Pendergrass, was as follows: "There are multiple annular shadows, which simulate cavities, and which may be thin-walled cavities. There is some thickening of the apical pleura, with displacement of the trachea toward the right. I can find no evidence of active disease at this time."

When this paper was written (June 15, 1935) the patient was working at manual labor. His only complaint was dyspnea on exertion.

The essential features of these four cases are summarized in the table.

Cases of Chronic Pulmonary Infection Due to the Friedländer Bacillus

Case No.	Age	Sex	Race	Location of Lesion	Type of Anatomic Distribution	Complications	Ultimate Result
1 J. A.	50	M	Italian	Upper, middle and lower lobes of right lung	Lobular	Formation of multiple abscesses throughout the right lung	Living 7 years later; no respiratory symptoms
2 M. P.	50	F	English	Upper and lower lobes of left lung	Lobar	Formation of large abscess in upper lobe of left lung	Death from venous thrombosis and sepsis two years after the attack of pneumonia following an attack of acute sore throat, apparently unrelated to earlier infection
3 T. M.	43	M	American Negro	Upper lobe of right lung; lower and upper lobes of left lung	Lobar	Formation of multiple abscesses in upper lobe of left lung	Unknown at the time of writing
4 J. J.	63	M	Italian	Upper lobe of right lung	Lobar	Formation of multiple abscesses in upper lobe of right lung	Working as a laborer two years later; marked dyspnea on exertion

COMMENT

The organism that was isolated from the sputum of the first three patients and from the blood and sputum of the fourth was a gram-negative nonmotile bacillus, with a large, easily stained capsule. It formed large, moist, semitranslucent mucinous colonies when cultured on blood agar. It produced acid and gas in dextrose and usually in saccharose. It caused little or no fermentation of lactose; it did not produce indole; it gave rise to slight acidity in milk, without coagulation;

it did not liquefy gelatin. Thus, it would be considered to be one of the S variants in Julianelle's [4] classification. He obtained from pure capsulated S strains noncapsulated R strains by cultivation in broth containing 10 per cent of homologous immune serum. Recent work [5] has shown the importance of the capsule in determining the virulence of a strain and that cultures of the same species show great differences, depending on their age, the method of cultivation and other factors which affect the formation of capsules.

The literature contains ample reference to the acute, rapidly fatal form of pneumonia caused by this organism. Recently Bensley [6] reported the clinical and pathologic findings in a 42 year old man who died on the sixth day of the attack. Fremmel, Henrichsen and Sweany [7] reported clinical and pathologic data on the case of a 49 year old man who died twenty-six hours after the onset of the acute pulmonary infection. Olcott [8] described the lesions in six patients who died in New York. In five of his patients culture of blood obtained at autopsy revealed the Friedländer bacillus; in the sixth the organism was cultured from the lung. In all six cases the course was acute, death occurring in from two to ten days after the onset of acute symptoms. All the patients were men between 38 and 55 years of age; four were white and two were Negroes. Three had a definite history of alcoholism, and three had a history of chronic infection of the upper respiratory tract. In four instances there was pneumonia of lobar distribution; in one, pneumonia of the lobular type, and in one, lobar distribution in one lobe and lobular in another. In five instances a typically mucinous appearance was seen on cross-section. The pulmonary alveolar walls were more or less injured in all.

---

4. Julianelle, L. A.: (*a*) A Biological Classification of Encapsulatus Pneumoniae (Friedländer's Bacillus), J. Exper. Med. **44**:113, 1926; (*b*) Immunological Relationships of Encapsulated and Capsule-Free Strains of Encapsulatus Pneumoniae (Friedländer's Bacillus), ibid. **44**:683, 1926; (*c*) Immunological Relationships of Cell Constituents of Encapsulatus Pneumoniae (Friedländer's Bacillus), ibid. **44**:735, 1926.

5. (*a*) Bensted, H. J., and others: A System of Bacteriology in Relation to Medicine, Medical Research Council, London, His Majesty's Stationery Office, 1929, vol. 4, p. 286. (*b*) Kliewe, H.: Epidemiologische und biologische Studien über den B. pneumoniae Friedländer und verwandte Arten, Zentralbl. f. Bakt. (Abt. 1) **116**:92, 1930. (*c*) Neuber, E.: Uber spezifische Schutzstoffe des mit Kapselbakterien (Sklerom-Ozaena-Friedländer-Bacillen) infizierten Organismus, Arch. f. Dermat. u. Syph. **170**:154, 1934.

6. Bensley, E. H.: A Case of Friedländer's Pneumonia, Canad. M. A. J. **26**:681, 1932.

7. Fremmel, F.; Henrichsen, K. J., and Sweany, H. C.: Pneumonia from Friedländer's Bacillus, Ann. Int. Med. **5**:886, 1932.

8. Olcott, C. T.: Pneumonia Due to Friedländer's Bacillus, Arch. Path. **16**: 471 (Oct.) 1933.

Most writers have stressed the rarity of the Friedländer bacillus as the causative agent of pneumonia in infancy and early childhood. Comba [9] reported such a case in 1896, the organism being obtained in pure culture from the blood of the heart and from exudate from the lungs. In 1915 Dunn and Hammond [10] reported an instance of pneumonia with recovery in a 14½ month old boy. The condition clinically presented the features of lobar pneumonia, first of the lower lobe of the left lung with crisis, and then a reinfection of the upper lobe of that lung. While thoracentesis was being attempted, the exploring needle entered the underlying lung, no fluid being obtained from the pleural cavity. Bacteriologic examination of the contents of the lumen of the exploring needle revealed a pure culture of a gram-negative encapsulated bacillus. The organism corresponded in morphologic structure and in all cultural characteristics to B. mucosus-capsulatus. This case is apparently the first in which recovery was reported in America from pneumonia due to the Friedländer bacillus.

Kliewe [5b] reported from Germany an epidemic of pneumonia due to the Friedländer bacillus in a home caring for one hundred and thirty children. Two children died. B. mucosus-capsulatus seemed to be the sole etiologic agent for the fatal and nonfatal pulmonary lesions. The larger epidemic in Germany, reported by Zander [11] in 1919, has been referred to previously.

Ferguson and Tower [12] in 1933 described pneumonia due to the Friedländer bacillus in twins 7 months old, a girl and a boy. The girl contracted the disease first and died on the eighth day. The boy became ill two days after the onset of the illness in his sister, but he completely recovered after thirty-two days' hospitalization.

Already the literature reveals the appreciation that the chronic sequelae of the acute pneumonic process may strongly suggest, clinically and roentgenographically, chronic pulmonary tuberculosis. From this standpoint the case of Westermark [13] is of particular interest. Brulé, Huguenin, and Gilbert-Dreyfus [14] reported the clinical course, and

9. Comba: Friedländer's Pneumonie-Mikrokokkus, Jahresb. ü. d. Fortschr. v. d. Path. Microorg. **12**:101, 1896.

10. Dunn, C. H., and Hammond, J.: A Case of Friedländer's Pneumonia with Recovery, Interstate M. J. **22**:1133, 1915.

11. Zander, A.: Ausgedehnte Endemie von Lungenentzündungen durch Infektion mit Friedländerschen Pneumobazillen unter Zivilarbeitern, Deutsche med. Wchnschr. **45**:1180, 1919.

12. Ferguson, J. A., and Tower, A. A.: Pneumonia in Infants Due to Bacillus Mucosus-Capsulatus, Am. J. Dis. Child. **46**:59 (July) 1933.

13. Westermark, N.: Ein Tuberkulose vortäuschender Fall von Friedländer's Pneumonie mit lange sich hinziehendem Verlauf, Acta radiol. **7**:626, 1926.

14. Brulé, M.; Huguenin, R., and Gilbert-Dreyfus: Pneumopathie chronique à bacilles de Friedländer, Bull. et mém. Soc. méd. d. hôp. de Paris **51**:1370, 1927.

Brulé, Huguenin and Foulon [15] reported the pathologic observations of a chronic pulmonary infection due to the Friedländer bacillus in a woman aged 34. Her illness extended over nine years. A vaccine prepared from the Friedländer bacillus apparently produced some temporary benefit.

Schlapper [16] described the illness of a woman aged 30, which extended over two years. Permission for autopsy could not be obtained. This case is of particular interest because the culture of the Friedländer bacillus obtained from the sputum, contrary to what usually occurs, was overgrown by pneumococci, staphylococci and streptococci. Schlapper concluded that in his case a strain of the Friedländer bacillus less virulent than that usually encountered had been the causative agent. Sweany, Stadnichenko, and Henrichsen [17] in 1931 described the clinical and bacteriologic observations in a chronic pulmonary infection with the Friedländer bacillus fatal after twenty-eight months. The organism differed from that ordinarily described in that it grew as well or better anaerobically as aerobically, it grew poorly on potato medium, it fermented lactose, producing acid and gas, and it produced coagulation in milk. The clinical aspects closely simulated chronic pulmonary tuberculosis, differing from it only in the general appearance of the patient, the irregularity in temperature and the obscure physical observations. The roentgen observations resembled those noted in chronic pulmonary tuberculosis. Toward the end of this patient's illness the odor of the sputum became increasingly offensive. My associates and I have not encountered this feature in any of our four cases.

Gerhartz,[18] in 1933, reported eight cases in which the patient survived the acute stage of the disease. Five patients were men, aged, respectively, 56, 72, 69, 64 and 34; three were women, aged 59, 28 and 30. One of these patients, a man aged 69, died three months after the onset of the illness. In addition to containing the Friedländer bacillus, the sputum was reported to contain pneumococci and numerous spirilla. Two other patients had mixed infections. Two patients, men aged 56 and 34, had an antecedent fibrous pulmonary tuberculosis. There was activation of the tuberculosis by the pneumonic process. One patient, a woman aged 59, evidently contracted the disease from her brother, aged 69, with whom she lived. Gerhartz' eighth patient, a nurse aged

15. Brulé, M.; Huguenin, R., and Foulon, P.: Etude anatomo-clinique d'une pneumopathie chronique due au bacille de Friedländer, Ann. d'anat. path. **4**:889, 1927.

16. Schlapper, K.: Ueber Friedländer-Pneumonien, Beitr. z. Klin. d. Tuberk. **78**:741, 1931.

17. Sweany, H. C.; Stadnichenko, A., and Henrichsen, K. J.: Multiple Pulmonary Abscesses Simulating Tuberculosis, Arch. Int. Med. **47**:565 (April) 1931.

18. Gerhartz, H.: Friedländer-Pneumonie, Med. Klin. **27**:147, 1933.

30, presumably contracted the disease from the sixth patient, a 34 year old man. Her pneumonia was complicated by an infection of the urinary tract, both the Friedländer bacillus and the colon bacillus being cultured from the urine.[4b] In the reports of these cases no mention was made of studies of blood cultures.

The first case reported in the literature in which the Friedländer bacillus was cultured from the sputum and from the blood during life seems to be that of Phillipi.[19] The patient was described as "a robust old man." Death occurred shortly after his admission to the hospital. Phillipi felt that no similar case had previously been reported.

Apelt [20] reported ten cases in patients aged, respectively, 42, 46, 51, 50, 30, 53, 50, 38, 74 and 44. All the patients were men except two. The condition ended fatally in all the cases except case 4. In cases 1 and 2 the Friedländer bacillus was cultured from both the sputum and the blood. The one patient who recovered had four sterile blood cultures. From the sputum of this patient, in addition to the Friedländer bacillus, staphylococci were cultured. Apelt concluded that, to his knowledge, case 4 in his series was the first case of pneumonia bacillus due to the Friedländer in which the patient had recovered.

In America the case of Dunn and Hammond [10] seems to be the first reported instance of recovery. This case is also of interest as one of the early cases in which bacteriologic diagnosis was possible by means of lung puncture. However, apparently it was not done purposely, as has been suggested by Horder.[21]

DIAGNOSIS

The leukocyte counts of our first three patients were all above normal, though they were less than those seen in the usual case of pneumococcic lobar pneumonia. The actual counts are given in a former paper.[1e] The temperature, pulse rate, respiratory rate and leukocyte curves in case 4 are given in figure 4. At *A* the Friedländer bacillus was isolated from the blood stream. At *B* the blood culture was sterile. In four of Olcott's [8] cases, the blood counts showed less than 7,000 leukocytes; in one of these the number was less than 2,000, with 24 per cent large mononuclears.

During the acute stage all our patients had bloody mucoid sputum, not particularly malodorous, in fairly large amounts. From this sputum we succeeded repeatedly in culturing the Friedländer bacillus in pure culture or as the predominant organism. The organism obtained from

19. Phillipi, E.: Ein Fall von kruppöser Pneumonie und Sepsis, hervorgerufen durch den Pneumobazillus Friedländer, München. med. Wchnschr. **49**:1884, 1902.

20. Apelt, F.: Ueber die durch den Bacillus Pneumoniae Friedländer hervorgerufene Pneumonie, München. med. Wchnschr. **55**:833, 1908.

21. Horder, T.: Lung Puncture: A New Application of Clinical Pathology, Lancet **2**:1345, 1909.

the blood in case 4 seemed to be biologically identical with that isolated simultaneously from the sputum. The patient in case 1, who has been under observation for over seven years, and the patient in case 4, who has been under observation for over two years, raise no sputum at the time of writing. Culture of material from their throats reveals no Friedländer bacilli. In none of our patients, either in the acute or in the chronic stage, have we resorted to puncture of the lung [21] as an aid in diagnosis. Repeated examinations have never disclosed tubercle bacilli in the sputum of any of the patients.

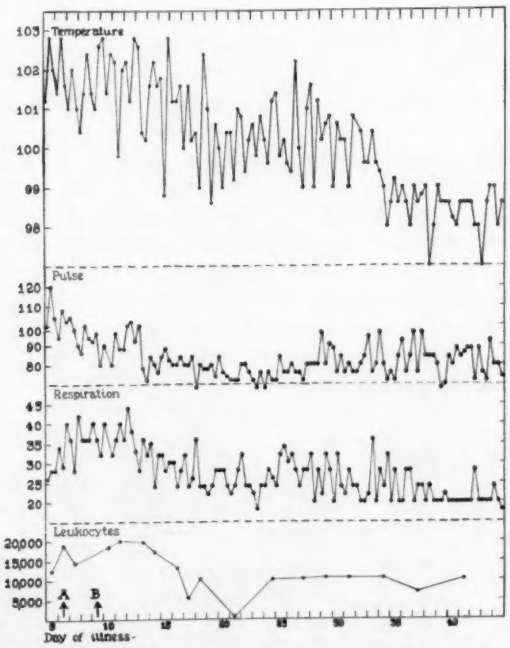

Fig. 4 (case 4).—At *A*, B. mucosus-capsulatus was recovered in pure culture from the blood stream. At *B*, the blood culture was sterile.

All our patients at some stage have shown formation of the cavities (table 1). Roentgenologically, it has appeared that the cavity walls are thin. This is in keeping with the observations of Westermark [13] and of Gerhartz [18]: "Large thick-walled cavities do not suggest Friedländer pneumonia." However, in reporting their case, Sweany, Stadnichenko and Henrichsen [17] stated that "the roentgen observations resembled those noted in chronic pulmonary tuberculosis."

TREATMENT

The treatment of our patients consisted of comfortable rest in bed. Resort was not made even to postural drainage. Several patients whose cases are reported in the literature have had surgical drainage of the pulmonary lesion. In Apelt's [20] case in which the patient recovered he apparently was well eighteen days after operation. Schlapper's [16] patient died shortly after operation.

The use of an autogenous vaccine by Brulé, Huguenin and Gilbert-Dreyfus [14] has been referred to previously. The preparation of a bacteriophage by Caublot [22] and the immunologic studies of Neuber [5e] concerning specific protective substances following infection with the Friedländer bacillus may in the future prove therapeutically useful.

SUMMARY

Follow-up data are presented concerning three previously reported cases of recovery from pneumonia due to the Friedländer bacillus. One of these patients was still living over seven and one-half years after the attack of pneumonia. One patient died of an apparently unrelated infection two years after the attack of pneumonia. The third patient we have been unable to locate.

A fourth case of recovery is reported. In this case the Friedländer bacillus was isolated from both the sputum and the blood during the acute stage of the pneumonia. This patient is now doing manual labor, over two and one-half years after the attack of pneumonia. At the site of the original pneumonic lesion there are still marked clinical and roentgenologic signs.

The end-result of pneumonia due to the Friedländer bacillus, both clinically and roentgenologically, almost completely simulates chronic pulmonary tuberculosis in that it produces cavitation, displacement of the trachea, elevation of the domes of the diaphragm and elevation of the hili of the lungs.

---

22. Caublot, P.: Le bacteriophage du pneumobacille de Friedländer, Compt. rend. Soc. de biol. **90**:622, 1924.

CONVULSIVE SEIZURES IN ADULT LIFE

A. EARL WALKER, M.D.
NEW HAVEN, CONN.

One of the most startling and to the laity most terrifying symptoms of disease is a fit. Particularly is this true when the afflicted person is an adult, for convulsive attacks in children are not infrequently observed even by the layman. When an adult who has apparently been in perfect health has an epileptiform attack it creates such a vivid impression on the witnesses that a physician is consulted at once. The latter has not an easy task, for to ferret out the etiologic agent producing an epileptic attack in an adult who has never previously had a convulsive seizure demands the keenest clinical acumen. While idiopathic epilepsy is common in childhood, it becomes rarer as age increases, and, as Oppenheim [1] stated, "We must always be on our guard when the epilepsy develops during adult life."

Epilepsy is merely a symptom complex or, as Foerster [2] said, a special form of reaction of the central nervous system. In order to explain why certain persons with organic lesions of the brain have epileptic seizures while others, with just as severe lesions, do not, some authorities have hypothesized a special "x" factor, or convulsive capacity, for persons having seizures. It seems simpler, however, to assume that any one's nervous system might react with a seizure were the stimulus sufficiently intense. In other words, the convulsive capacity is a pathophysiologic reaction of the central nervous system, the threshold of stimulation to which varies. In the person with idiopathic epilepsy the threshold is low, and a slight upset in the regulation of the normal bodily activities is sufficient to cause a convulsion.

A convulsion may be produced either by increasing the intensity of stimulation until it reaches the convulsive threshold or by lowering the threshold to a level at which a lesser stimulus is effective. The first method is illustrated when galvanic stimulation of the cortex produces

---

From the Department of Neurology and Surgery of the University of Iowa.

Read before the combined meeting of the medical societies of Johnson, Iowa, Cedar, Muscatine, Louisa and Washington counties at the University of Iowa, May 1, 1935.

1. Oppenheim, H.: Textbook of Nervous Diseases, Edinburgh, The Darien Press, 1911, vol. 2, p. 1424.

2. Foerster, O.: Die Pathogenese des epileptischen Krampfanfalles, Deutsche Ztschr. f. Nervenh. **94**:15, 1926.

fits, and the second, when hyperventilation produces an alkalosis which increases the irritability of the central nervous system. In some cases the factors that cause these changes are known, and the condition is spoken of as symptomatic epilepsy; in other cases, in which the disturbing factor is unkown, the term idiopathic epilepsy is used.

In this paper the factors responsible for convulsions in the adult will be discussed. A series of a hundred patients with epilepsy beginning in adult life, admitted to the service of Dr. Clarence E. Van Epps at the University Hospitals, will be analyzed. Besides the routine physical and laboratory examination, a complete neurologic study, including an examination of the cerebrospinal fluid, roentgenographic examination of the skull and in many of the cases of idiopathic epilepsy encephalography, was made to determine any possible organic etiology for the attacks. No cases of petit mal alone or localized twitching were included. All the patients had had major attacks, although four had not had a clonic convulsion and their condition was classified as major epilepsy sine agitatione.

TABLE 1.—*The Age Incidence and Etiology of Epilepsy Occurring for the First Time in Adult Life in One Hundred Patients*

Etiologic Factor	Age					
	20-29	30-39	40-49	50-59	60-	Total
Idiopathic	21	17	9	0	0	47
Tumor of the brain	4	5	5	2	0	16
Neurosyphilis	4	5	5	1	0	15
Hypertension and arteriosclerosis	0	1	3	5	5	14
Trauma	3	0	1	0	0	4
Miscellaneous	1	2	1	0	0	4
Total	33	30	24	8	5	100

Table 1 shows the final diagnosis in the cases and the age incidence of the types of epilepsy. It is obvious from a perusal of this table that while idiopathic epilepsy is the most common type occurring in adult life it becomes rarer as age increases and after 40 constitutes only 21 per cent of all cases. The highest incidence of epilepsy due to syphilis of the central nervous system or to tumor of the brain occurs at the age when those diseases have their greatest frequency. As would be expected, epileptiform convulsions as a manifestation of hypertension and cerebral arteriosclerosis occur in late adult life.

If the types are analyzed to determine the total number and frequency of attacks (table 2), it at once becomes evident that idiopathic epilepsy has greater frequency and causes many more attacks than epilepsy with demonstrable intracerebral pathologic changes. It is also apparent that a considerable number of the patients with organic lesions had only one or two convulsions. The difference between the types may be due to several factors. In the first place, other evidence of cerebral dysfunc-

tion causes the patient with an organic lesion to report to the physician before many attacks have occurred. In many cases, however, only one or two attacks occur over a period of several years; so it must be assumed that the symptomatic variety does not have the periodicity which is characteristic of idiopathic epilepsy. It is interesting to note that the incidence of petit mal is much higher in idiopathic than in symptomatic epilepsy.

A consideration of the pathologic conditions which manifest themselves at times by epileptic attacks [3] will be of assistance in a further analysis of the cases under consideration.

TABLE 2.—*The Frequency and the Total Number of Attacks, According to the Etiology of the Epilepsy*

Etiologic Factor	Number of Attacks			Frequency of Attacks		Type	
	1	2 to 10	Over 10	Less than 1 per Mo.	More than 1 per Mo.	Minor	Jacksonian
Idiopathic	0	7	40	19	28	20	3
Tumor of the brain	4	10	2	12	4	3	2
Neurosyphilis	1	9	5	10	5	3	..
Hypertension and cerebral arteriosclerosis	1	9	4	13	1	1	2
Trauma	0	0	4	4	0	..	1
Miscellaneous	0	3	1	4	0	..	..

TUMOR OF THE BRAIN

Convulsive seizures are not infrequent manifestations of cerebral neoplasm. Sargent [4] reported an incidence of convulsions of 30.9 per cent in a series of 270 patients. Parker [5] in a series of 313 patients with cerebral tumor found that 67 (21.4 per cent) had major epileptic convulsions. Dowman and Smith [6] found that seizures occurred in 39 per cent of 100 cases of intracranial growth. In a statistical survey of Bailey's cases from the University of Chicago, Ley and Walker [7] found that 25.7 per cent of the patients suffering from tumor of the brain had generalized convulsions.

3. (*a*) Brock, Samuel: The Convulsive State, Arch. Neurol. & Psychiat. **20**:420 (Aug.) 1928. (*b*) Cobb, Stanley: Causes of Epilepsy, ibid. **27**:1245 (May) 1932. (*c*) Lennox, W. G., and Cobb, Stanley: Epilepsy, Harvard Medicine Monographs, Baltimore, Williams & Wilkins Company, 1928, p. 197.

4. Sargent, Percy: Some Observations on Epilepsy, Brain **44**:312, 1921.

5. Parker, H. L.: Epileptiform Convulsions, Arch. Neurol. & Psychiat. **23**:1032 (May) 1932.

6. Dowman, E. C., and Smith, W. A.: Intracranial Tumors, Arch. Neurol. & Psychiat. **20**:1312 (Dec.) 1928.

7. Ley, A., and Walker, A. Earl: Statistical Review of Two Hundred and Thirty Intracranial Tumors, Rev. de cir. de Barcelona **10**:197 (Oct.) 1935.

The frequency of epileptic manifestations varies considerably with the site and the type of intracranial neoplasm. A tumor of the temporal, parietal or frontal lobe produces seizures more frequently than one in another region (Gibbs [8] and Groff [9]). It has been stated that glioma is more prone to cause epileptic attacks than meningioma, but Groff found that 30.9 per cent of patients with meningioma had fits—an incidence certainly as high as that in all cases of tumor of the brain or all cases of glioma. The truth of Groff's statement is more apparent than real, for while approximately one third of all gliomas occur in the posterior fossa, less than 10 per cent of meningiomas (Groff [9] and Elsberg [10]) occur there. Since it is well recognized that a lesion of the posterior fossa rarely causes epileptic attacks, a more accurate statistical report would be based on cases of supratentorial tumor. From such a report it would be obvious that the incidence of epilepsy with glioma is somewhat higher than that with meningioma.

That a convulsion may be the initial symptom of cerebral tumor is well known, and the symptomatology in approximately 15 per cent of all cases of tumor of the brain is ushered in by an epileptic seizure. (Parker [5] gave the percentage as 12.1; Dowman and Smith,[6] as 15, and Ley and Walker,[7] as 12.9.) Appreciation of this fact is of utmost importance if the rather gloomy outlook for the treatment of tumor of the brain is to be improved. The early recognition of an intracranial growth is essential if surgical therapy is to be effective, for by the time the diagnosis becomes evident to any tyro, the lesion is frequently so large that it cannot be removed without leaving the patient in a socially, if not an absolutely, helpless condition. At the time of the first convulsion many patients have sufficient neurologic abnormalities to make the correct diagnosis possible. There are, however, a certain number in whom no abnormalities can be found (in the present series, four of sixteen patients), and one must rely on accessory aids. Roentgenograms of the skull may show erosion or hyperostosis of the cranium or calcification within the neoplasm and thus make diagnosis possible. Such abnormalities unfortunately do not often accompany cerebral tumor. If no further examination were made, the diagnosis would be idiopathic epilepsy, and not until the onset of more ominous symptoms would the true condition be suspected.

---

8. Gibbs, F. A.: Frequency with Which Tumors in Various Parts of the Brain Produce Certain Symptoms, Arch. Neurol. & Psychiat. **28**:969 (Nov.) 1932.

9. Groff, Robert A.: The Meningioma as a Cause of Epilepsy, Ann. Surg. **101**:167, 1935.

10. Elsberg, Charles A.: The Parasagittal Meningeal Fibroblastomas, Bull. Neurol. Inst. New York **1**:389, 1931.

NEUROSYPHILIS

Convulsive attacks may occur as a result of involvement of the central nervous system in either the secondary or the tertiary stage of syphilis. Early in the secondary stage there is frequently a mild meningeal reaction, usually manifested only by headache but occasionally giving rise to a generalized convulsion. The more acute syphilitic meningitis, particularly that occurring over the vertex, not infrequently gives rise to fits. In the late secondary stage the meningovascular and cerebral types of syphilis occasionally manifest themselves by epileptic attacks. Tertiary lesions, particularly gumma and dementia paralytica, frequently cause seizures. The incidence of attacks in dementia paralytica has been estimated variously by different authors. Kraepelin [11] has expressed the belief that they occur in from 30 to 90 per cent of all cases. In some of the cases he described, however, the patient had only minor spells without a true loss of consciousness and without a clonic convulsion. Fournier [12] stated that convulsive seizures which appear for the first time in a patient when he is from 30 to 40 and apparently in good health are eight or nine times out of ten of syphilitic origin. This estimate is undoubtedly far too high, but it serves to emphasize the importance of Spirochaeta pallida as an etiologic factor in epilepsy beginning in adult life.

There are several suggestive distinguishing points between idiopathic epilepsy and epilepsy due to neurosyphilis. Nonne [13] observed that the intelligence suffers much less in the latter than in true epilepsy and that long remissions are characteristic. The second point is well illustrated in the present series, in which ten of the fifteen patients had less than five attacks, although the majority had had attacks over a longer period than one year.

In many cases epilepsy caused by neurosyphilis can be diagnosed clinically. A routine psychiatric and neurologic examination frequently shows sufficient abnormality to lead one to suspect a syphilitic involvement of the central nervous system even in the absence of a history of syphilitic infection. With the routine use of the Wassermann and the Kahn test of the blood the diagnosis is readily confirmed, for almost all patients with early secondary syphilis, gumma or dementia paralytica have a positive Wassermann reaction. As mentioned, these are the patients in whom convulsions are most common. In epilepsy due to

11. Kraepelin, E.: General Paresis, translated by J. W. Moore, Nervous and Mental Disease Monograph 14, New York, Nervous and Mental Disease Publishing Company, 1913, p. 200.

12. Fournier, A.: La syphilis du cerveau, Paris, G. Masson, 1879, p. 654.

13. Nonne, Max: Syphilis and the Nervous System for Practitioners, Neurologists and Syphilologists, translated by Charles R. Ball, ed. 2, Philadelphia, J. B. Lippincott Company, 1916, vol. 24, p. 450

other types of syphilitic involvement of the central nervous system—meningovascular syphilis, cerebral syphilis, etc.—in which the Wassermann reaction is not so frequently positive—the history, neurologic findings and course of the disease usually point to the correct diagnosis. Fourteen of the fifteen patients in the present series who had epileptiform attacks due to neurosyphilis, had markedly positive Wassermann and Kahn reactions of the blood. Thirteen had a Wassermann and a Kahn reaction of 4 +, and the fourteenth had a Wassermann reaction of 1 +, and a Kahn reaction of 3 +. The fifteenth patient died shortly after admission in status epilepticus, and a Wassermann test was not made.

HYPERTENSION AND ARTERIOSCLEROSIS

A great deal has been written on the rôle of hypertension and arteriosclerosis in the production of senile epilepsy, or epilepsia tarda.[14] In 1859 Kussmaul and Tenner [15] produced convulsions by jugular compression and severe bleeding and considered cerebral anemia one of the most important factors in the production of epileptic attacks. Their findings have been verified many times (Flesch [16] and Naunyn [17]), and cerebral anemia is still considered an important, if not the prime, factor in the production of seizures, particularly as several observers have seen the blanching of the cerebral cortex at operation just before a fit. The narrowing of the lumen of a vessel caused by arteriosclerosis undoubtedly is very important in producing cerebral anemia, but the anemia is produced slowly and so does not give rise to the same symptoms as does a rapidly produced anemia.[18] The theory most favored to explain the production of the cerebral anemia that is believed to occur when a fit is initiated is based on vasoconstriction. With the demon-

14. (*a*) Cross, Ernest S.: The Significance of Epileptiform Seizures Originating in Adult Life, M. Clin. North America **16**:1227 (March) 1933. (*b*) Matorine, O.: Senile Epilepsy, with the Report of Four Cases, Internat. Clin. **3**:174, 1928. (*c*) Osborne, O. T.: Epilepsy Late in Life, Ann. Int. Med. **1**:841, 1928. (*d*) Redwood, Frank H.: Senile Epilepsy (Epilepsia Tarda), Virginia M. Monthly **55**:804, 1929. (*e*) Savill, Thomas D.: Senile Epilepsy and the Vertiginous Attacks Which Supervene for the First Time in Advanced Life, Illustrated by a Case of Cardio-Arterial Hypertrophy, Lancet **2**:131, 1909. (*f*) Sympson, E. Mansel: Remarks on Senile Epilepsy, Brit. M. J. **1**:1069, 1894.

15. Kussmaul, A., and Tenner, A.: Epileptiform Convulsions Caused by Profuse Bleeding and Also True Epilepsy, translated by E. Bronner, London, New Sydenham Society, 1859.

16. Flesch, J.: Die Auslösung von Anfällen durch Karotiden Kompression, Wien. klin. Wchnschr. **28**:1422, 1915.

17. Naunyn, B.: Ueber senile Epilepsie, Ztschr. f. klin. Med. **28**:217, 1895.

18. Gildea, E. F., and Cobb, Stanley: The Effects of Anemia on the Cerebral Cortex of the Cat, Arch. Neurol. & Psychiat. **23**:876 (May) 1930.

stration of nerve fibers along the cerebral vessels [19] and vasoconstriction by stimulation of cervical sympathetic fibers,[20] the theory has been further emphasized. Lange [21] observed that there is very little vasoconstrictor reaction in sclerosed vessels, and so some other mechanism must be present if arteriosclerosis is an important cause of epilepsy. Krapf,[22] however, pointed out that simple senile changes in the brain and arteriosclerosis cannot be important factors, for epilepsy rarely begins or is present at the age (that is, over 70) at which such changes are most prevalent. He also noted that while arteriosclerosis was a prominent concomitant in a group of patients with late epilepsy, it was not the most common factor either clinically or at autopsy. Increased blood pressure with marked fluctuations was present in 85 per cent of his cases, and he concluded that this was the most important factor. In support of his contention he quoted Lange, who had observed that vascular constriction was more pronounced and more readily produced in a hypertensive than in a normal state. Most American writers (Elliott,[23] Reisman and Fitz-Hugh,[24] and Redwood [14d]) place equal emphasis on hypertension and arteriosclerosis. Oppenheimer and Fishberg,[25] however, expressed the belief that hypertension is the important factor not only in hyperpiesia but also in uremia and lead poisoning.

Only three of the fourteen patients in the series under discussion with hypertension or arteriosclerosis of the brain had definite and marked peripheral arteriosclerosis. Five had evidence of cerebral thrombosis and softening and probably had marked cerebral vascular thickening. Ten had a blood pressure above 150 systolic. If 150 is considered the upper limit of normal, then the most common factor in this group is vascular hypertension. In some cases the vascular instability noted by Krapf [22] was seen.

---

19. Penfield, W.: Intracerebral Vascular Nerves, Arch. Neurol. & Psychiat. **27**:30 (Jan.) 1932.

20. Forbes, H. S., and Wolff, H. G.: Cerebral Circulation: II. The Vasomotor Control of Cerebral Vessels, Arch. Neurol. & Psychiat. **19**:1057 (June) 1928.

21. Lange, F.: Die Funktion der Blutstrombahn bei Arteriosklerose, Deutsches Arch. f. klin. Med. **157**:320, 1927; Die Funktion der Blutstrombahn bei Hypertonie, ibid. **158**:214, 1928.

22. Krapf, E.: Ueber Spätepilepsie, Arch. f. Psychiat. **97**:323, 1932.

23. Elliott, Arthur R.: Epilepsia Tarda—Convulsive Cerebral Crises in High Blood Pressure and Arteriosclerosis, M. Clin. North America **17**:1469, 1934.

24. Reisman, D., and Fitz-Hugh, J.: Epilepsia Tarda, Ann. Int. Med. **1**:273, 1927.

25. Oppenheimer, B. S., and Fishberg, A. M.: Hypertensive Encephalopathy, Arch. Int. Med. **41**:264 (Feb.) 1928. Fishberg, A. M.: Hypertension and Nephritis, Philadelphia, Lea & Febiger, 1934, p. 668.

TRAUMA

The great war gave an opportunity for the study of the relation of cerebral injury to epilepsy. The incidence of convulsive seizures following major head injuries has been variously reported, at from 25 per cent (Rawling [26]) to less than 5 per cent (Sargent [4]). Wagstaffe [27] observed that epilepsy was much more frequent after penetrating wounds of the dura than after other head injuries, and as a corollary Turner [28] found marked neurologic defects in many cases. The frequency of posttraumatic epilepsy appears greater the longer the period in which the cases are followed, for many patients do not have fits for from five to fifteen years after a head injury (Stevenson [29]). Wagstaffe and Adie,[30] who studied the immediate effect of head injuries, stated that epileptic attacks occur in only 5 per cent of cases and are due to cerebral contusion, laceration, edema or hemorrhage, subarachnoid, subdural or extradural. The patients are not more likely than other persons to have epilepsy later. Turner [28] found that in twenty-five of thirty-six cases in which the time of the first attack was known it occurred within the first year and in the remainder before the lapse of two and one-half years. He noted that fits tend to occur at longer intervals in posttraumatic epilepsy than in the idiopathic variety. Stevenson [29] stated that mental deterioration is more common in posttraumatic epilepsy.

In the four cases included in this report in which the diagnosis was posttraumatic epilepsy, the epilepsy appears to have had a direct relation to cerebral trauma. In all four the cerebral laceration was visualized at operation. Three patients underwent encephalography, which showed abnormalities. In the fourth case roentgenograms of the skull showed a foreign body within the brain substance. The shortest period between the accident and the first attack was three days and the longest interval one and one-half years. Two patients had their first attack on the fourth day and the forty-fifth day, respectively. One patient included in the group with idiopathic epilepsy might have been placed in the class with posttraumatic seizures. He was a man of 26 who four years before admission had suffered a severe head injury in an automobile accident, which had rendered him unconscious for fourteen hours. After an uneventful convalescence he was well for two and one-half years and

26. Rawling, L. B.: Gunshot Wounds of the Head, Brit. J. Surg. **10**:93, 1922.

27. Wagstaffe, W. W.: The Incidence of Traumatic Epilepsy After Gunshot Wounds of the Head, Lancet **2**:861, 1928.

28. Turner, W. A.: Epilepsy and Gunshot Wounds of the Head, J. Neurol. & Psychopath. **3**:309, 1923.

29. Stevenson, W. E.: Epilepsy and Gunshot Wounds of the Head, Brain **54**:214, 1931.

30. Wagstaffe, W. W., and Adie, W. J.: Notes on a Series of One Hundred and Sixty-One Cases of Gunshot Wounds of the Head Treated at No. 7 General Hospital, May to August 1916, J. Roy. Army M. Corps **31**:307, 1918.

then began to have grand and petit mal attacks about once a month. Physical and neurologic examination gave negative results, and encephalograms showed merely slight dilatation of the lateral ventricles. It is such cases that are difficult to classify; undoubtedly this patient suffered marked cerebral disturbance at the time of his accident which conceivably was sufficient to initiate his attacks.

MISCELLANEOUS CONDITIONS

Numerous conditions, both of the central nervous system and of the somatic organs, may manifest themselves in convulsions. Foerster [2] listed the conditions of the central nervous system which may be accompanied by convulsions as follows: congenital disease of the brain, heredodegenerative processes, traumatic lesions, presence of tumor, parasites, syphilis, tuberculosis, cerebral abscess, swelling of the brain, meningitis, leptomeningitis, chronic arachnoiditis, juvenile encephalitis, epidemic encephalitis, multiple sclerosis, presenile gliosis, senile cortical degeneration, toxic conditions and disturbances of circulation. Many of these conditions have already been discussed; some are peculiar to childhood and have no place in this article. The conditions in which epilepsy may occur in adult life are as follows:

- Intracranial pathologic conditions
  - Degenerative
    - Pick's disease
    - Alzheimer's disease
  - Inflammatory
    - Meningitis
      - Acute: syphilitic and pyogenic
      - Chronic: granulomatous
    - Pachymeningitis: haemorrhagica interna
    - Encephalitis
      - Chronic
        - Epidemic
        - Multiple sclerosis
        - Syphilitic
      - Acute
        - Suppurative
        - Nonsuppurative
        - Abscess of brain
        - Sequelae
    - Parasitic disease: hydatid cyst and cysticercosis
    - Thrombosis of the longitudinal sinus [31]

31. Grinker, Roy R.: Neurology, Springfield, Ill., Charles C. Thomas, Publisher, 1934, p. 979.

- Traumatic
  - Cerebral contusions and lacerations: (*a*) edema; (*b*) scarring [32]
  - Subarachnoid hemorrhage
  - Subdural hematoma
  - Middle meningeal hemorrhage
  - Electrocution
- Vascular
  - Arteriosclerosis and hypertension
  - Cerebral thrombosis, embolism and hemorrhage
  - Cerebral vascular spasm
  - Raynaud's disease
  - Angioneurotic edema [33]
  - Cerebral aneurysm
- Neoplastic
  - Glioma
  - Meningioma
  - Metastatic brain tumor
  - Vascular tumor: angioma
  - Other intracranial neoplasms

General somatic diseases

- Metabolic [34]
  - Protein sensitization
    - Intrinsic
    - Extrinsic
  - Heat stroke
- Respiratory
  - Pleural epilepsy
  - Hyperventilation
  - Asphyxia from any cause
- Cardiovascular
  - Hypertension
  - Subacute bacterial endocarditis
  - Stokes-Adams' syndrome
  - Paroxysmal tachycardia
  - Cardiac decompensation
  - Disease of carotid sinus
- Alimentary
  - Constipation (chronic intestinal intoxication)
- Renal: uremia
- Endocrine
  - Thyroid: hypothyroidism
  - Pancreas: hypoglycemia, spontaneous and induced
  - Adrenals: hypersecretion
  - Thymus

---

32. Kenyon, James H.: Traumatic Epilepsy (with Discussion), Ann. Surg. **64**:731, 1916.

33. Bassoe, P.: Angioneurotic Edema of the Brain, M. Clin. North America **15**:409 (Sept.) 1932. Oliaro, T.: Ueber cerebrale Symptome bei angioneurotischen Odem, Klin. Wchnschr. **12**:1185, 1933.

34. Wirth, O.: Zur Pathogenese des epileptischen Krampfanfalls: Stoffwechselpathologie, Ztschr. f. d. ges. Neurol. u. Psychiat. **109**:521, 1927.

- Parathyroids: hypoparathyroidism
- Pituitary
  - Hyperpituitarism
  - Hypopituitarism
- Gonads
  - Menstruation
  - Pregnancy
  - Menopause
- Blood dyscrasias
  - Pernicious anemia
  - Hemorrhage
- Intoxication
  - Bacterial
    - Botulism
    - Tetanus
  - Metabolic
    - Uremia
    - Toxemia of pregnancy
    - Acute yellow atrophy
  - Extraneous
    - Water
    - Alcohol
    - Cocaine
    - Camphor
    - Lead
    - Arsphenamine
    - Picrotoxin
    - Magnesium sulfate
    - Strychnine
    - Absinth
    - Thujone
    - Caffeine
    - Ergot
    - Nicotine
    - Epinephrine
- Psychogenic

The congenital diseases of the brain which cause epileptic seizures, and not all do, usually do so long before the person reaches adult life. The same is true of the heredodegenerative diseases. There are, however, two abiotrophies in which convulsive seizures are not uncommon—Pick's and Alzheimer's disease. In the former, convulsions are not common (Thorpe [35]) and usually occur only in the later stages of the disease, at which time a diagnosis is not difficult. In Alzheimer's disease, in which convulsions are more common (Henderson [36]) and occur earlier in the course of the disease, the differential diagnosis is more difficult, and accessory aids may be necessary.

35. Thorpe, F. I.: Pick's Disease (Circumscribed Senile Atrophy) and Alzheimer's Disease, J. Ment. Sc. **78**:302, 1932.

36. Henderson, D. K.: Alzheimer's Disease, J. Ment. Sc. **76**:646, 1930.

Inflammatory lesions of any part of the central nervous system may give rise to convulsions. A generalized seizure may usher in either acute purulent or chronic meningitis of tuberculous, syphilitic or blastomycetic origin. During the course of such meningitis in children fits are common, but in adults, rarer. In suppurative encephalitis (abscess of the brain) they occur both during the acute stage and, more commonly, as a sequela of the damage to the brain.[37] In the present series there was a case of abscess of the brain—secondary to a pulmonary abscess—in which convulsions were the first symptom.

Epilepsy is rarely seen as a symptom of chronic epidemic encephalitis (von Economo [38]) or of multiple sclerosis.[39]

Parasites within the central nervous system not infrequently produce epileptic seizures, which differ in no way from those occurring in idiopathic epilepsy. The type of parasite most commonly found is the cysticercus; hydatid cyst is rare. The former in the late stages of the disease becomes calcified and may be seen in roentgenograms of the skull. Calcification of the cyst also occurs in muscles and may be demonstrated particularly in the muscles of the thigh by the roentgenologist. Frequently, small nodules are palpable in the skin; a biopsy of these reveals the cysticercosis (Dixon and Smithers [40]).

Toxins and toxic agents not infrequently cause epileptic seizures. In the late stages of botulism fits may occur. One type of ergotism (Barger [41]) is characterized by involvement of the central nervous system, and convulsions are frequent with it. Numerous drugs (Cobb [3b])—cocaine, strychnine, magnesium sulphate, picrotoxin, absinth, thujone, camphor, caffeine, nicotine, lead and epinephrine—occasionally give rise to convulsive seizures. The relation of alcohol to epilepsy is still debatable, but it is certain that the indulgence in alcohol by persons with epilepsy increases the frequency of attacks. There seems to be sufficient evidence for one to assume that in some cases epilepsy is due to acute [42] or chronic alcoholism.

---

37. Holden, W. B.: Epilepsy Occurring Twenty Years After Operation for Brain Abscess, S. Clin. North America **11**:1027, 1931. Adson, Alfred W., and Craig, W. McK.: The Surgical Management of Brain Abscess, Ann. Surg. **101**:7, 1935.

38. von Economo, C.: Encephalitis Lethargica: Its Sequelae and Treatment, translated and adapted by K. O. Newman, London, Oxford University Press, 1931, p. 200.

39. Sachs, B., and Friedman, E. D.: General Symptomatology of Multiple Sclerosis, A. Research Nerv. & Ment. Dis., Proc. **2**:49, 1921.

40. Dixon, H. B. F., and Smithers, D. W.: Epilepsy in Cysticercosis (Taenia Solium), Quart. J. Med. **3**:603, 1934.

41. Barger, George: Ergot and Ergotism, London, Gurney & Jackson, 1931, p. 279.

42. Yawger, N. S.: Alcoholism and Epilepsy, Also So-Called Acute Alcoholic Epilepsy, Am. J. M. Sc. **147**:735, 1914.

Almost every known disease is occasionally associated with fits, but unless the concurrence is considerably greater than three in a thousand cases, which is the general rate of occurrence of epilepsy, the association cannot be considered more than coincidental. This fact must be borne in mind when the relation of somatic diseases to the convulsive state is discussed.

Endocrine disturbances have long been blamed for the production of epileptic seizures.[43] When, however, the evidence is critically reviewed, there is found to be little ground for the theory. Dysfunction of the thyroid has been suggested as the basis of seizures, but the occurrence of fits with hyperthyroidism is rare (Lennox and Cobb[3c]), and clinical hypothyroidism is not present with seizures, though 25 per cent of persons with epilepsy have a low rate of oxygen consumption (Lennox and Wright[44]). The relationship of the parathyroids to epilepsy is more interesting. Redlich[45] reviewed a series of cases in which tetany and epilepsy coexisted. He found that after the surgical removal of the parathyroids symptoms of tetany appeared at once but generalized convulsion did not appear for months. Other authors (Curschman[46] and Fischer and Leyser[47]) have suggested a common basis for the two conditions, but there is little evidence for this view. Hyperfunction of the adrenals has been said to be the causative factor in some cases. Convulsions may be produced by the injection of epinephrine but do not appear as symptoms of the adrenal cortical syndrome (Walters, Wilder and Kepler[48]). There is more evidence that the pituitary gland plays a rôle in the causation of fits.[49] Epileptic attacks are not uncommonly a symptom of a pituitary tumor[50]; in Cushing's[51]

43. Limer, J. H.: Endocrine Dyscrasias in the Production of Epileptic States, New York M. J. **114**:16, 1921.

44. Lennox, W. G., and Wright, L. H.: Studies in Epilepsy: VII. The Basal Metabolism, Arch.Neurol. & Psychiat. **20**:764 (Oct.) 1928.

45. Redlich, E.: Tetanie und Epilepsie, Monatschr. f. Psychiat. u. Neurol. **30**:439, 1911.

46. Curschman, H.: Epilepsie und Tetanie, Deutsche Ztschr. f. Nervenh. **61**:1, 1918.

47. Fischer, H., and Leyser, E.: Epilepsie und Tetanie, Monatschr.f.Psychiat. u. Neurol. **52**:213, 1922.

48. Walters, W.; Wilder, R. M., and Kepler, E. J.: The Suprarenal Cortical Syndrome with Presentation of Ten Cases, Ann. Surg. **100**:670, 1934.

49. Lowenstein, Paul L.: Relation of the Pituitary Gland to Epilepsy, Am. J. M. Sc. **163**:120, 1922. Tucker, B. R.: The Rôle of the Pituitary Gland in Epilepsy, Arch. Neurol. & Psychiat. **2**:192 (Aug.) 1919.

50. Shanahan, W. I.: A Case of Epilepsy Associated with Acromegaly, J. Nerv. & Ment. Dis. **34**:289, 1907.

51. Cushing, H.: The Pituitary Gland and Its Disorders, Philadelphia, J. B. Lippincott Company, 1912, p. 351.

series of ninety-eight cases eighteen patients had fits. Hypopituitary symptoms in persons with epilepsy have been described by many authors, and a certain percentage of patients have been benefited by the administration of the gland substance. Reports of thymic disease and epilepsy are few and usually are of cases in adolescents (Browning [52]). The relationship of the pancreas to convulsive seizures has frequently been discussed. Although the acidosis produced by diabetes tends to inhibit epileptic attacks, seizures do occasionally occur in patients suffering from diabetes. The phenomenon of hyperinsulinism, both spontaneous and induced, is frequently associated with fits and other epileptic states (Wilder [53]).

The relationship of the gonads, particularly in women, to epilepsy has been the subject of much controversy. The occurrence of epileptic attacks at menstruation [54] or during pregnancy is well known. Lennox and Cobb [3c] expressed the belief that the occurrence of convulsions at menstruation is explained by the increased nervous irritability which many women exhibit at that time. Cases are reported of cessation of attacks following hysterectomy or castration. In one case in the series under discussion the patient had had three attacks—each one during pregnancy. Eclampsia [55] is an associated condition, although some authors consider that the eclampsia is due to hypertension rather than to a circulating toxin or an endocrine disturbance.

In summary, one may say that while an altered state of endocrine function is not infrequently found in epilepsy, it is uncommon to find such a condition bearing an etiologic relation to the seizures.

Disease of other organs occasionally produces epileptic seizures. In spite of reports to the contrary (Reed [56]), the gastro-intestinal tract is in rare instances the cause of an epileptic attack. Diseases of the respiratory system likewise play a little rôle in the production of convulsive seizures. "Pleural epilepsy" (Abadie [57]) has been described. After a

52. Browning, W.: The Question of Thymic Epilepsy, with Report of a Demonstrative Case, M. Rec. **98**:1013, 1920.

53. Wilder, J.: Zur Neurologie und Psychiatrie der hypoglykämischen Zustände, Med. Klin. **26**:616, 1930.

54. Souques, A., and Gilbrin, E.: Crises mensuelles d'épilepsie apparues après la suppression spontanée et précoce de la menstruation, Rev. neurol. **2**:109, 1930. Gordon, Alfred: Convulsive Disorders of Two Opposite Periods of Life: Puberty and Climacterium, Am. J. Psychiat. **12**:929, 1933.

55. Campbell, W. E.: The Eclamptic Convulsion, Arch. Neurol. & Psychiat. **20**:425 (Aug.) 1928.

56. Reed, Charles A. L.: Some Typical Recoveries in Iowa from Chronic Convulsive Toxaemia (Epilepsy) Following Surgical Correction of the Abdominal Viscera, J. Iowa M. Soc. **10**:204, 1920.

57. Abadie, Jean: Modern Etiologic Conceptions of the Epilepsies, Rev. neurol. **1**:1041, 1932; abstr., Arch. Neurol. & Psychiat. **31**:1320 (June) 1934.

simple puncture of the pleura or pleural lavage, convulsive seizures have occurred. These are due to cerebral air or fluid embolism. In cases of mild involvement only syncopal attacks develop, but when the disease is severe status epilepticus may supervene. "Pleural epilepsy" is, however, rare. Hyperventilation may, by causing alkalosis, induce tetany or, more rarely, convulsions. In a small proportion of persons with epilepsy (25 per cent) an attack may be brought on by hyperventilation. Diseases of the circulatory system frequently initiate epileptic fits. Instances of convulsive attacks in Stokes-Adams' disease are numerous (Finny,[58] Russell [59] and Clark [60]). Attacks are seen occasionally in patients suffering from paroxysmal tachycardia (Clark [60]). They are of either the grand or the petit mal type. It is considered that they are due to cerebral anemia. In the present series there was a case of convulsive seizures associated with subacute endocarditis, the fits probably being due to cerebral emboli.

In uremic states with hypertension due to chronic nephritis, convulsions are common and may occur with few premonitory symptoms of the disease. The diagnosis may not be apparent if the patient is seen first at the time of the convulsion, but an analysis of the blood and the urine, together with the finding of hypertension, is usually sufficient to enable the physician to make the correct diagnosis. However, the presence of albumin in the urine does not necessarily indicate renal damage, as many persons with idiopathic epilepsy have albuminuria after an attack. Fishberg and Oppenheimer [25] consider the fits in uremia as due to hypertension and claim that they are rare in cases of uncomplicated uremia. Foster,[61] however, isolated a toxic base from the blood of uremic patients which produces convulsive seizures in experimental animals.

THE PSYCHOGENIC FACTOR

Much has been written on the psychogenic factor in epilepsy. Some authors consider it the most important causative agent. Row and Bond [62] gave numerous reports of cases showing its influence. However, it is generally conceded that while psychogenic factors are undoubtedly present in every case they are rarely the most important elements. Clark [63]

58. Finny, J. M.: Bradycardia, with Arrhythmia and Epileptiform Seizures, Brit. M. J. **1**:967, 1906.

59. Russell, Alfred E.: Some Disorders of the Cerebral Circulation and Their Clinical Manifestations, Lancet **1**:963, 1909.

60. Clark, F. H.: Occurrence of Epileptoid Attacks in Tachycardia and Bradycardia, Brit. M. J. **2**:308, 1907.

61. Foster, Nellis B.: Uremia, J. A. M. A., **76**:281 (Jan. 29) 1921.

62. Row, R. G., and Bond, W. E.: Epilepsy: A Functional Mental Illness and Its Treatment, New York, Paul B. Hoeber, Inc., 1926, p. 138.

63. Clark, L. P.: Psychology of Essential Epilepsy, J. Nerv. & Ment. Dis. **63**:575, 1926.

and Rosett [64] both present interesting theories as to the psychogenic etiology of epilepsy.

IDIOPATHIC EPILEPSY IN ADULT LIFE

Gowers [65] stated that in only 20 per cent of cases of idiopathic epilepsy does the condition begin in adult life. Study of the cases under consideration shows that less than half of all patients having epileptic attacks for the first time in adult life suffer from the idiopathic type. After the age of 50 that variety of epilepsy is practically unknown. In a person over 20 the diagnosis of idiopathic epilepsy is made only when every possible etiologic factor has been eliminated. Even then a careful watch is necessary for any further developments which might indicate that an organic cause has been overlooked.

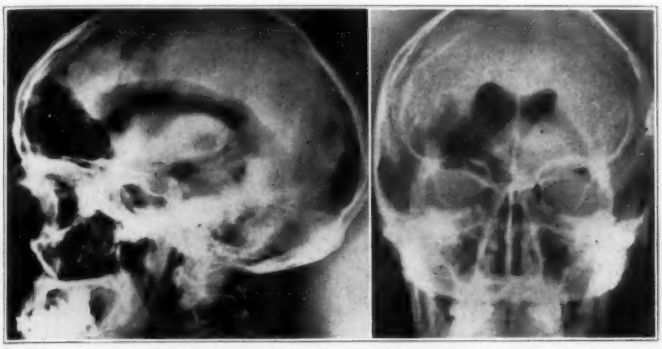

Fig. 1.—Encephalograms of a patient in whom convulsive seizures developed after an injury to the head. Although both the physical and the neurologic examination gave essentially negative results, the encephalograms reveal a large cyst of the left frontal lobe.

Every adult presenting himself with the complaint of convulsive seizures should have a history taken with special reference to the disorders previously discussed and a complete physical and neurologic examination, as well as the routine laboratory tests, including a Wassermann and a Kahn test of the blood. If no abnormalities are revealed, roentgenograms of the skull should be taken. With such an examination the organic etiologic factors will be demonstrated in a majority of cases. A small percentage of patients, however, may harbor unrevealed gross intracranial pathologic conditions. For this reason it is advisable to

64. Rosett, J.: The Mechanism and Fundamental Cause of the Epilepsies, Arch. Neurol. & Psychiat. **9**:689 (June) 1923.

65. Gowers, W. R.: Epilepsie and Other Chronic Convulsive Diseases, London, J. & A. Churchill, 1881.

perform encephalography or ventriculography on every patient in whom there is no apparent cause for the seizures. Encephalographic findings frequently substantiate a provisional diagnosis or are sufficiently clear to make a definite diagnosis.

Thus, when clinical methods have been exhausted, encephalography enables the physician in a large percentage of cases to discover the organic etiologic factor when one exists. In posttraumatic epilepsy, encephalography usually reveals ventricular distortion or dilatation or some abnormality in the subarachnoid spaces. Foerster and Penfield [66] described the typical ventricular distortion as a wandering ventricle, the ventricle being drawn up at one point by scar tissue, with a subsequent shift of the entire ventricular system to that side. Occasionally a large cerebral cyst, such as the one illustrated in figure 1, is found.[67] Cere-

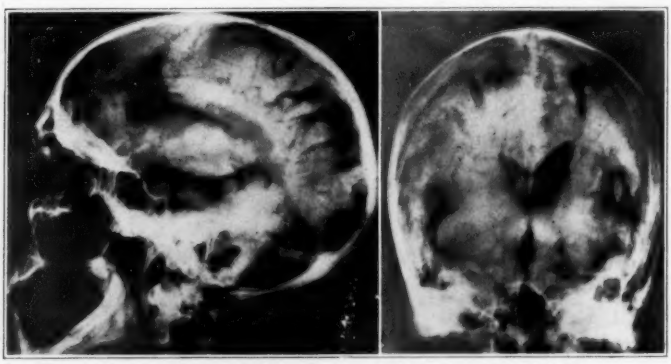

Fig. 2.—Encephalograms of a patient who had five generalized convulsions over a period of seventeen years. After the last attack, two years previous to his admission to the hospital, he had marked verbal aphasia and transient hemiparesis, of the right side. The encephalograms show an area of cortical atrophy in the distribution of the left prerolandic artery, probably due to scarring secondary to thrombosis of that vessel.

bral pathologic changes due to cerebral arteriosclerosis or degenerative disease of the central nervous system may be shown by encephalography when the changes are sufficient to produce an alteration in the shape or size of the cerebrum. The cerebral scarring secondary to a vascular accident is frequently well shown in an encephalogram (fig. 2). Occa-

66. Foerster, O., and Penfield, W.: Der Narbenzug am und im Gehirn bei traumatischer Epilepsie in seiner Bedeutung für das Zustandekommen der Anfälle und für die therapeutische Bekämpfung derselben, Ztschr. f. d. ges. Neurol. u. Psychiat. **125**:475, 1930.

67. Dr. Percival Bailey, of the University of Chicago Clinics, permitted the use of the encephalograms accompanying this article.

sionally, in the absence of any evidence of intracranial hypertension, a cerebral neoplasm is found by encephalography (fig. 3). Intracranial pneumography allows a differentiation between two or more possible etiologic factors. Head injuries are so common now that there are few persons who have not suffered from cerebral concussion at some time, and yet to accept such an injury arbitrarily as an etiologic factor would lead to numerous errors. It is well known that many patients suffering from cerebral tumor date their symptoms from a head injury. The fact that a patient has a positive Wassermann reaction of the blood is no indication that he may not have an intracranial neoplasm, and if the course of his condition under therapy is not satisfactory, studies with air of his intracranial cerebrospinal fluid system may show the reason for the lack of response. Cerebral vascular disease is particularly difficult to distinguish from tumor in many cases. A slowly progressive loss of

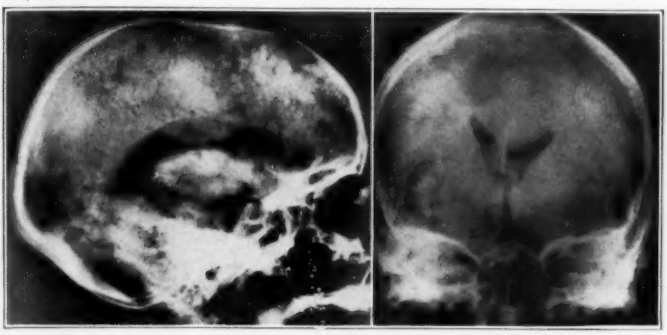

Fig. 3.—Encephalographic findings in a case of parasagittal glioma producing epileptic attacks initiated by a tingling sensation of the right hand.

cerebral function points to a neoplastic condition, but frequently it is necessary to resort to encephalography to make a definite diagnosis. Hypertension is not uncommonly associated with cerebral tumor, and hence one must not be content with a diagnosis of hyperpiesia with symptomatic epilepsy, particularly if there are any atypical features.

If ventricular filling does not occur when encephalography is performed, it is essential to perform ventriculography, for one cause of nonfilling of the ventricles is the presence of an intracranial neoplasm. Even though considerable air is visualized in the subarachnoid spaces over the cerebral cortex (fig. 4), a neoplasm maay be present. Such findings have been encountered in several patients in whom subsequent ventriculography showed evidence of a cerebral tumor. For this reason any case of nonfilling of the cerebral ventricles during encephalography

should be considered a reason for suspecting tumor of the brain and a ventriculography should be performed.

With the aid of tests with air one can make a definite diagnosis in some cases, and in those instances in which the encephalogram reveals no abnormalities one may be fairly well satisfied that an etiologic factor which might be treated surgically has not been overlooked. Hence encephalography is a valuable adjunct to the diagnostic armamentarium of the neurologist or neurosurgeon in attacking the problem of the etiology of convulsive seizures originating in adult life. It enables him to diagnose or practically to eliminate tumor of the brain as an initiator of the attacks. By localizing the epileptogenous zone in cases of post-traumatic epilepsy it enables him to employ the method of cortical extirpation suggested by Foerster and Penfield [66] for the relief of

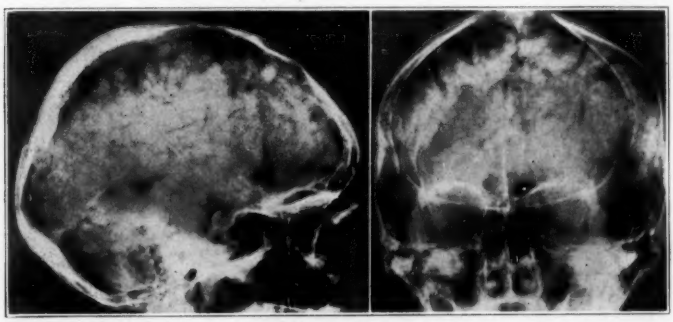

Fig. 4.—Anteroposterior and lateral encephalograms showing a large amount of air over the cerebral cortex, with an absence of ventricular filling, in a case of tumor of the left temporal lobe with symptomatic epilepsy.

symptoms. In still other cases it presents evidence which may be the necessary confirmation of a clinical opinion.

SUMMARY

The conditions associated with convulsive seizures occurring for the first time in adult life in a series of one hundred cases are enumerated. While in by far the largest number of cases the etiologic factor was not known in many cases the patient was suffering from tumor of the brain, neurosyphilis or vascular hypertension with or without arteriosclerosis.

The conditions in which epilepsy may occur symptomatically are tabulated and discussed.

Encephalography is suggested as a valuable diagnostic adjunct which should be employed before a condition is pronounced idiopathic epilepsy.

MORPHOLOGIC CHANGES IN THE HEART IN EXPERIMENTAL MYXEDEMA

BRUCE WEBSTER, M.D.
AND
CRISPIN COOKE, B.A.
NEW YORK

Cardiac enlargement and changes indicative of low voltage in the electrocardiogram have long been recognized as a part of the clinical picture of myxedema in the human being. The mechanism of the production of these signs is not well understood. With the introduction of the operation of total thyroidectomy as a therapeutic measure in chronic heart disease,[1] a knowledge of the exact nature of the changes which occur in the heart as a result of myxedema becomes of vital importance. With this in mind, experiments were planned which would enable us to study the effects of long-standing myxedema experimentally induced in animals. In the medical literature on the subject there is some confusion as to whether there are specific pathologic changes in the heart muscle in myxedema and still greater confusion as to whether these changes are responsible for the increase in the size of the heart and the changes of voltage in the electrocardiogram.

Ord [2] in 1880 described the heart of a patient with myxedema as being hypertrophied, flabby and dilated. Since then various cases have been reported, with a variety of pathologic changes. These include atheromatous changes in the large blood vessels, edematous swelling of the aortic leaflets, scars in the myocardium and edema of the heart muscle. Several authors, on the other hand, have denied the presence of any pathologic change in the heart in myxedema. These cases have recently been summarized by Ohler and Abramson.[3] Wegelin [4] in 1926

From the Barbara Henry Research Laboratory of the Department of Medicine of the New York Hospital and Cornell University Medical College.

1. Blumgart, H. L.; Riseman, J. E. F.; Davis, D., and Berlin, D. D.: Therapeutic Effect of Total Ablation of the Normal Thyroid on Congestive Heart Failure and Angina Pectoris: III. Early Results in Various Types of Cardiovascular Disease and Coincident Pathologic States Without Clinical or Pathologic Evidence of Thyroid Toxicity, Arch. Int. Med. **52**:165, 1933.

2. Ord, W. M.: Tr. Clin. Soc. London **13**:15, 1880.

3. Ohler, W. R., and Abramson, J.: The Heart in Myxedema, Arch. Int. Med. **53**:165, 1934.

4. Wegelin, C., in Henke, F., and Lubarsch, O.: Handbuch der speziellen pathologischen Anatomie und Histologie, Berlin, Julius Springer, 1926, vol. 8, p. 353.

said: "The morphologic changes in the heart muscle in myxedema are not yet well understood." He further suggested that these apparent myocardial changes are due less to changes in the myocardium than to a decrease in the number of red blood cells and to bradycardia.

Several attempts have been made to study the pathologic changes resulting from myxedema experimentally induced in animals. Cretinism and myxedema have been confused in some of these studies, with the result that conclusions in regard to myxedema have been drawn on the findings produced by thyroidectomizing very young animals. There is wide disagreement in these experimental results.

Tatum [5] studied the histologic changes produced by thyroidectomy in rabbits weighing from 150 to 250 Gm. He reported degeneration of the myocardium, with swelling of the individual muscle cells. Benson [6] thyroidectomized adult rabbits and detected slight granular degeneration of the heart muscle. He considered these changes relatively slight. Kishi [7] thyroidectomized cats and dogs and noted little change in the histologic appearance of the heart muscle. Brooks and Larkin [8] reported no alteration in the myocardium of thyroidectomized adult rabbits. However, their animals were kept for a relatively short period. Goldberg [9] in 1927 studied the changes produced by thyroidectomy in the cardiovascular systems of young sheep. He noted calcification of the aorta and cardiac dilatation in these myxedematous animals but apparently was not impressed by any cytologic change in the heart muscle.

METHODS

The following experiment was planned in an effort to determine whether definite morphologic changes can be produced in the heart muscle of adult rabbits as a result of myxedema and if possible to ascertain the significance of these changes.

Four litters consisting of sixteen young adult Belgian rabbits weighing between 1,800 and 2,400 Gm. were divided into two groups. Five animals were set aside as controls. Three died during operative procedures. The remaining eight were successfully subjected to total thyroidectomy. The operation was performed with the animal under ether anesthesia. The thyroid isthmus was dissected free from the trachea and divided. The lobes were then removed separately, care being taken to avoid the recurrent laryngeal nerves and to free completely the superior poles of the gland. These animals made an uneventful postoperative recovery.

5. Tatum, A. L.: J. Exper. Med. **17**:636, 1913.
6. Benson, W.: Virchows Arch. f. path. Anat. **170**:229, 1902.
7. Kishi, K.: Virchows Arch. f. path. Anat. **176**:260, 1904.
8. Brooks, H., and Larkin, J.: Am. J. M. Sc. **155**:66, 1918.
9. Goldberg, S. A.: Quart. J. Exper. Physiol. **17**:15, 1927.

All the animals were maintained in individual cages and were fed a standard diet of alfalfa hay, oats and water, with green vegetables twice a week. The body weights were determined weekly. The rabbits of both the control and the thyroidectomized series remained in good health throughout the experiment.

Within three weeks after operation, the thyroidectomized animals began to show clinical evidence of myxedema. The fur became thin, and later actual bare areas developed. The movements were sluggish. No peripheral edema was noted. After some weeks there appeared to be an increase in the size of the abdomen. The myxedematous animals tended to gain weight more rapidly than those of the control series. The blood cholesterol level was used as an index of the severity of the myxedema. Approximately three months after operation three of the animals appeared to be recovering from the myxedema. Their blood cholesterol levels became normal. With the animal under ether anesthesia, the thyroid region was explored. Small areas of regenerated thyroid tissue were found in the region of the isthmus. These were removed by dissection and cautery, and the animals were returned to the experimental group. They again began to show clinical signs of myxedema at the end of from two to three weeks.

Electrocardiographic tracings were taken at intervals throughout the experiment for both the control and the experimental animals. The changes in voltage of the QRS complex and the height of the T wave were used as an adjunct to the clinical findings, and the blood cholesterol level was used as an index of the degree of myxedema and the state of the cardiac musculature. The three standard leads were employed. Contact was made by moistening the closely clipped legs with a solution of sodium chloride and wrapping them in wet flannel bandages, around which were several turns of copper wire to which the leads were attached.

The experiment was terminated from five to seven months after thyroidectomy. The animals were killed by carbon monoxide gas in a respiration chamber. Autopsy was performed immediately. The heart was removed; the great vessels were cut at a constant length, and all the blood contained in the chambers was allowed to drain out. The weight of the heart was taken. A segment of ventricle approximately 2 cm. square was then removed and weighed. This was dried for three days at 40 C. and again weighed. The loss of weight was used as a basis for the calculation of the fluid content of the heart. Tissue was taken from all organs of the body for microscopic examination. Segments were removed from both the left ventricle and the auricle of the heart in all animals. These were stained with hematoxylin and eosin and with sudan IV.

RESULTS

The control series of animals showed no abnormal changes at autopsy. The cardiac weights are shown in table 1. Microscopic examination showed normal heart muscle (figs. 1 and 2). All other organs were normal.

The changes in the myxedematous animals, on the other hand, were striking. There was some variation in the degree of myxedema present. Three animals (106, 107 and 108) were extremely myxedematous. Their blood cholesterol levels ranged between 305 and 330 mg. per hundred cubic centimeters. In the remaining five the condition was moderately severe but did not reach the stage of causing

effusions into the serous cavities of the body. They all showed a marked decrease in the amount of hair. Actual bald areas existed on several of the animals. There was no peripheral edema. The region of the neck was searched for evidence of thyroid tissue. In two of the rabbits (100 and 111) a cluster of cells approximately 1 mm. square was found over the trachea. Three animals (106, 107 and 108) showed several cubic centimeters of fluid in the pericardial cavity. These same animals each had approximately 150 cc. of fluid in the abdominal cavity. The

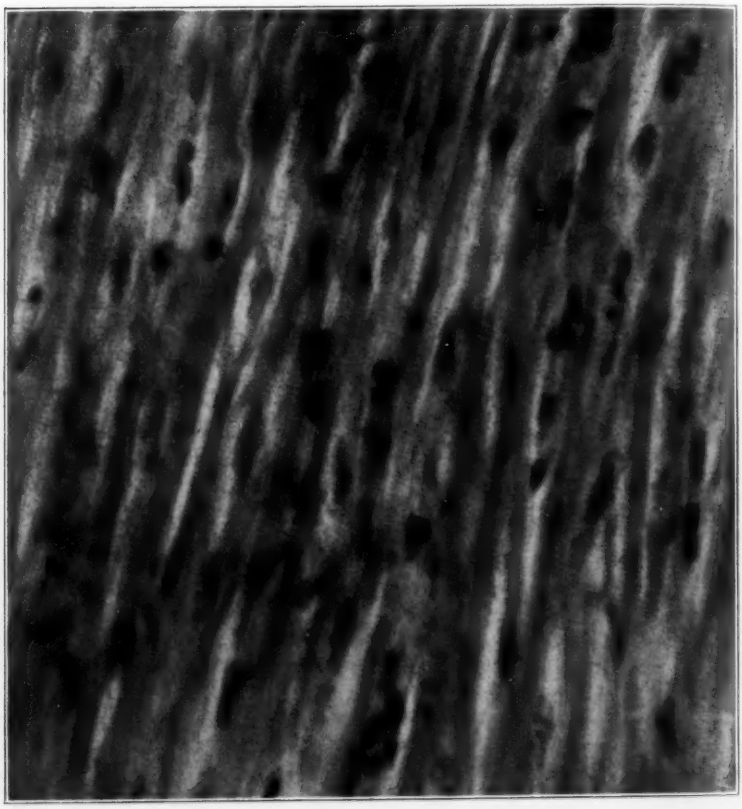

Fig. 1.—Photomicrograph of the heart muscle of rabbit 101, a normal control (× 700).

hearts of all the myxedematous animals were pale and flabby, in comparison with those of the normal controls. No changes were observed in the aorta. There were some fatty degeneration of the liver and marked atrophy of the germinal epithelium of the testes and the follicular portion of the ovaries.

The fluid content of the heart muscle, as determined by desiccation of a segment, is shown in table 1. The average percentage of fluid in the myxedematous

hearts was 81.9, while in the control series it was 75.6. The fluid content was highest in the three animals which showed the greatest clinical evidence of myxedema.

Microscopic Examination.—The heart muscle of the myxedematous animals took the hematoxylin and eosin stain less well than did that of the normal control animals. There was a striking increase in the size of the spaces between the individual fibers. The fibers themselves were swollen, and there was a decrease

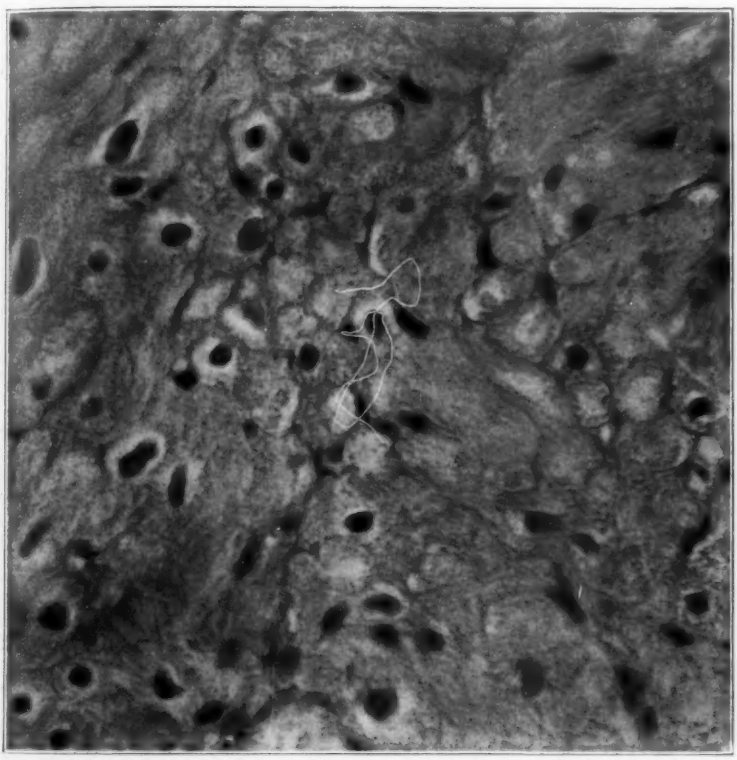

Fig. 2.—Photomicrograph of the heart muscle of rabbit 101, a normal control, showing fibers in cross-section (× 700).

in the actual number of fibers per square millimeter. There was an increase in prominence of the longitudinal striation and partial disappearance of the transverse striation. The nuclei were surrounded by a clear space and were pyknotic, tending to stain deeply. This increase in the perinuclear space is shown clearly in a cross-section of the muscle bundle (fig. 3). Frozen sections stained with sudan IV showed that there was little fat in the heart muscle. The clear spaces around the nuclei and between the fibers did not contain fat.

No definite changes could be made out in the aortas of the myxedematous animals. There was a definite atrophy of the germinal epithelium of the testes in the males and of the follicular portion of the ovaries in the females. There was some increase in the eosinophilic element of the pituitary. No other constant changes were observed in the myxedematous animals.

Electrocardiographic Findings.—The electrocardiographic tracings were intended primarily as an index of the degree of myxedema. In general, the voltage, as indi-

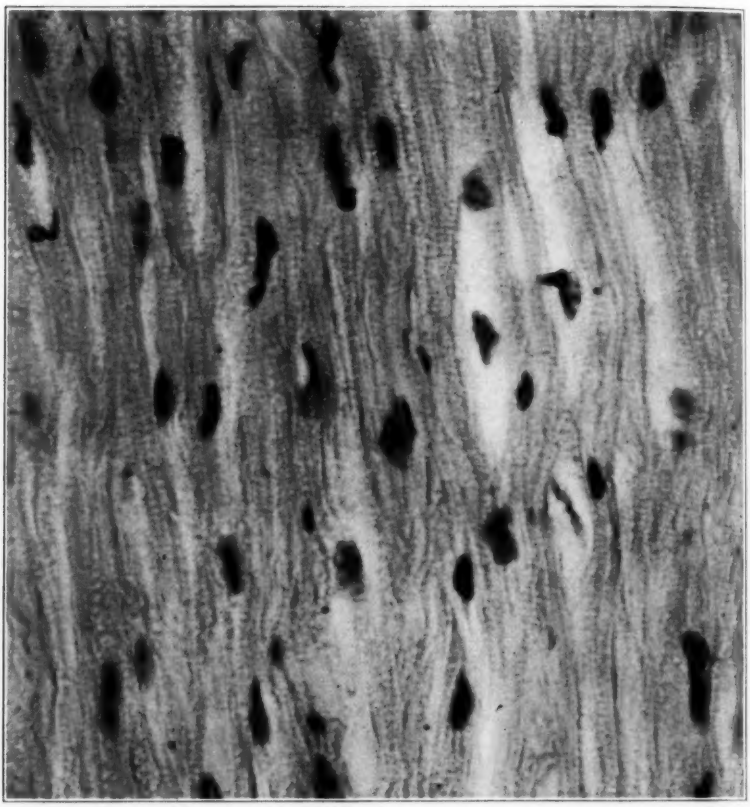

Fig. 3.—Photomicrograph of the heart muscle of rabbit 106, showing changes produced by myxedema (× 700).

cated by the changes in the height of the T wave and of the QRS complex, decreased with the development of the myxedema. These findings, however, were not as constant as would be expected from the present knowledge of myxedema in human patients. This may have been due to faulty or inconstant contacts of the various leads.

Protocol.—The protocol of one animal is given in detail. The observations on the others are summarized in table 2.

RABBIT 106.—An adult female Belgian rabbit was admitted to the laboratory on July 1, 1934. The weight was 1,750 Gm. Total thyroidectomy with the animal under ether anesthesia was performed on July 10, 1934. On Aug. 23, 1934, it was

TABLE 1.—*Weight and Fluid Content of the Hearts of Control and Thyroidectomized Rabbits*

Rabbit No.	Body Weight, Gm.	Weight of Heart, Gm.	Heart Weight-Body Weight Ratio	Percentage of Fluid in Heart Muscle
		Control Series		
101	3,425	7.36	465.3	77.6
102	3,144	7.28	433.2	74.3
103	3,355	7.31	458.9	76.2
104	2,700	7.10	340.3	75.8
110	3,425	7.19	476.4	74.2
		Thyroidectomized Series		
100	2,830	6.87	412.0	81.7
105	2,900	6.29	461.0	79.6
106	2,691	5.65	476.3	83.8
107	3,159	5.74	550.4	84.4
108	2,857	5.71	500.4	84.8
109	2,380	4.67	509.6	79.8
111	2,800	6.40	437.9	80.1
112	2,500	4.62	541.1	81.0

TABLE 2.—*Summary of Changes Observed at Autopsy*

Rabbit No.	Number of Days Since Operation	Clinical State	Gross Observations (Other Than Heart)	Microscopic Observations (Extent of Myocardial Changes)
100	142	Moderate myxedema	Minute area of thyroid tissue over trachea	Moderate degeneration
105	188	Moderate myxedema	.....	Moderate degeneration
106	185	Extreme myxedema	Fluid in pericardial sac and peritoneum	Marked degeneration
107	175	Extreme myxedema	Fluid in pericardial sac and peritoneum	Marked degeneration
108	178	Extreme myxedema	Fluid in pericardial sac and peritoneum	Marked degeneration
109	180	Moderate myxedema	.....	Moderate degeneration
111	119	Moderate myxedema	Minute area of thyroid tissue over trachea	Moderate degeneration
112	153	Moderate myxedema	.....	Moderate degeneration

noted that the animal had several bald spots and that its coat was dull and unhealthy looking. On Nov. 1, 1934, it had a definite mangy appearance. The cholesterol content of the blood at that time was 305 mg. per hundred cubic centimeters. The animal was killed on Jan. 12, 1935, one hundred and eighty-five days after operation. The body weight at that time was 2,691 Gm.

At autopsy the hair was scanty and lacked luster. The abdomen was distended. No thyroid tissue was found. The thymus gland was atrophic. There was no pleural effusion.

The pericardium was distended with clear fluid. The heart was flabby and soft. It weighed 5.65 Gm. and contained 83.8 per cent of fluid.

The abdomen contained several hundred cubic centimeters of clear fluid. The adrenal glands were within the normal weight range. All other organs were grossly normal.

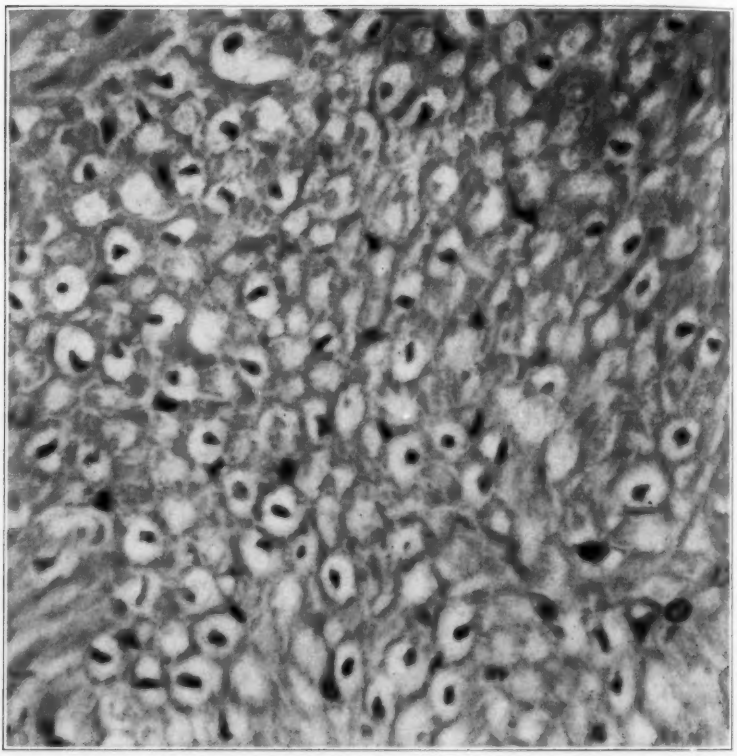

Fig. 4.—Photomicrograph of the heart muscle of rabit 106, showing changes produced by myxedema in cross-section of fibers (× 700).

SUMMARY

Myxedema was readily produced in adult rabbits by total removal of the thyroid gland. In the cases of more severe involvement this was accompanied by pericardial and peritoneal effusions. The heart muscle of these myxedematous animals had an average fluid content of 81.9

per cent, as compared with 75.6 per cent in a control series of normal animals. On microscopic examination this heart muscle showed marked degenerative changes, characterized by a decrease in the number of fibers, edema and a disappearance of the perinuclear sarcoplasm.

Myxedema is apparently capable of producing serious myocardial damage in the adult rabbit.

EFFECT OF ALKALINE THERAPY FOR PEPTIC ULCER ON UTILIZATION OF DIETARY IRON IN THE REGENERATION OF HEMOGLOBIN

FREDERICK KELLOGG, M.D.*
AND
STACY R. METTIER, M.D.
SAN FRANCISCO

Loss of blood over a long period leads to hypochromic anemia, which may properly be attributed to depletion of the iron stored in the body. Regeneration of hemoglobin in patients with uncomplicated anemia of this type occurs after cessation of the hemorrhage with the aid of appropriate iron therapy. One of the frequent causes of this type of anemia is prolonged or recurrent loss of blood from a peptic ulcer. In patients with depletion of stored iron due to a bleeding ulcer, dietary iron alone is insufficient to stimulate rapid formation of hemoglobin, and chronic anemia often persists after the bleeding is stopped.

A common method of treating peptic ulcer is the modified Sippy regimen. This requires the use of large amounts of alkaline powders daily over a long period. Such treatment obviously renders alkaline the contents of the upper part of the gastro-intestinal tract. In recent years it has been shown that an alkaline p_H of the gastro-intestinal tract is unfavorable for the absorption of metallic substances, such as calcium and phosphorus, and Mettier and Minot [1] have shown that small doses of iron are better utilized from an acid duodenal content than from a neutral or alkaline one. In addition, Reimann and Fritsch [2] and Bethell, Goldhamer, Isaacs and Sturgis [3] have reported that iron is more rapidly effective in patients with normal gastric secretion than in those with achlorhydria.

---

* Research Fellow of the American College of Physicians.
From the Division of Medicine, University of California Medical School.
This study was aided by the Christine Breon Fund for Medical Research.

1. Mettier, S. R., and Minot, G. R.: The Effect of Iron on Blood Formation as Influenced by Changing the Acidity of the Gastro-Duodenal Contents in Certain Cases of Anemia, Am. J. M. Sc. **181**:25 (Jan.) 1931.

2. Reimann, F., and Fritsch, F.: Experimentelle und klinische Untersuchungen über die Wirkung des Ferrum reductum, Ztschr. f. klin. Med. **117**:304, 1931.

3. Bethell, F. H.; Goldhamer, S. M.; Isaacs, R., and Sturgis, C. C.: Diagnosis and Treatment of Iron-Deficiency Anemias, J. A. M. A. **103**:797 (Sept. 15) 1934.

Ordinarily, patients with peptic ulcer secrete a gastric juice high in acid content. It occurred to us, however, that alkalinization might influence unfavorably the utilization of dietary iron and thus account for prolonged periods of anemia. It seemed desirable, therefore, to study the production of hemoglobin during the ingestion of dietary iron in patients undergoing alkaline therapy for peptic ulcer. Accordingly, four patients were selected for observation whose reserves of iron had been depleted by recurrent loss of blood from the bowel.

TYPE OF PATIENTS AND METHOD OF STUDY

All four patients were men. They varied in age from 37 to 61 years. Each one gave a history of prolonged loss of blood from the gastro-intestinal tract. In one patient bleeding had been noticed for six months, and in the others, for one or more years. Prior to the starting of our investigation bleeding had stopped. The diagnoses of peptic ulcer were substantiated by roentgen ray examination.

The anemia was of the hypochromic type, and in none of the patients was there clinical evidence of infection or a malignant process that might account for it.

Fractional analyses showed the presence of free hydrochloric acid in the contents of the stomachs of all four patients during fasting.

Daily examinations of the blood were made, including estimations of the hemoglobin content and erythrocyte and reticulocyte counts. The concentration of hemoglobin was determined with a Sahli hemometer calibrated so that 100 per cent equaled 14 Gm. of hemoglobin per hundred cubic centimeters of blood. The stools were examined frequently for macroscopic and occult blood to determine whether or not hemorrhage recurred.

The clinical data for the patients studied are shown in the table.

Clinical Data

No.	Patient	Sex	Age	History	Gastric Secretion
1	R. B.	M	53	Duodenal ulcer with bleeding for one year; tarry stools for two months	Fasting, 4 cc. N/10 HCl per 100 cc.; after histamine, 11 cc. N/10 HCl per 100 cc.
2	W. D.	M	37	Duodenal ulcer with tarry stools for one year	Fasting, 5 cc. N/10 HCl per 100 cc.; after histamine, 55 cc. N/10 HCl per 100 cc.
3	J. McK.	M	61	Recurrent gastric ulcer; gastro-enterostomy one year previously; tarry stools for six months; generalized arteriosclerosis	Fasting, free HCl present
4	J. M. M.	M	60	Recurrent duodenal ulcer; hematemesis three years previously; gastro-enterostomy one year previously; tarry stools for one month	Fasting, 15 cc. N/10 HCl per 100 cc.; after histamine, 77 cc. N/10 HCl per 100 cc.

The method of alkalinizing the upper part of the gastro-intestinal tract was based on a modified Sippy regimen. It consisted of the administration of an alkaline powder every two hours throughout the day and of 200 cc. of whole milk or milk and cream at alternate hours. This diet is decidedly poor in iron. The total daily consumption of alkalis amounted to from 11 to 19 Gm. of sodium bicarbonate, from 3 to 5 Gm. of calcium carbonate and from 1 to 2 Gm. of magnesium oxide.

OBSERVATIONS

During the period of alkaline therapy and restriction of the intake of iron there was no significant increase in hemoglobin concentration (charts 1, 2, 3 and 4). The number of erythrocytes failed to increase

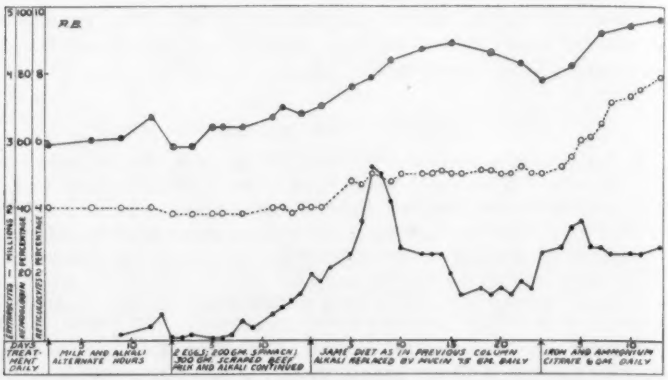
R.B.
MILK AND ALKALI ALTERNATE HOURS
2 EGGS; 200 GM. SPINACH; 300 GM. SCRAPED BEEF; MILK AND ALKALI CONTINUED
SAME DIET AS IN PREVIOUS COLUMN; ALKALI REPLACED BY MUCIN 7.5 GM. DAILY
IRON AND AMMONIUM CITRATE 6 GM. DAILY

Chart 1.—Curves showing the ineffectiveness of an iron-rich diet on the formation of hemoglobin in patient 1 while he was undergoing alkaline therapy, the moderate response after the withdrawal of alkalis and the increase in red blood cells after the addition of dietary iron. In the charts the curve of circles with X and a straight line indicates red blood cells in millions per cubic millimeter; the curve of circles and dashes, the percentage of hemoglobin content, and the curve of dots and a straight line, the percentage of reticulocytes.

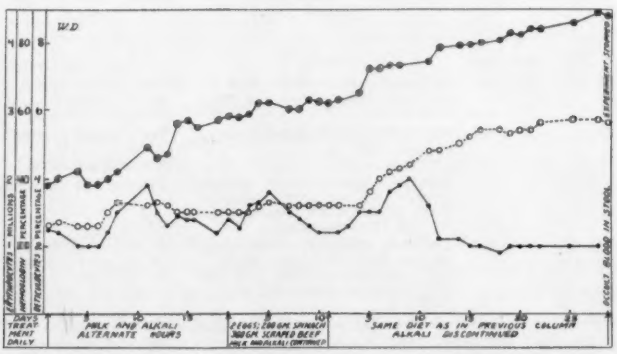
W.D.
MILK AND ALKALI ALTERNATE HOURS
2 EGGS; 200 GM. SPINACH; 300 GM. SCRAPED BEEF; MILK AND ALKALI CONTINUED
SAME DIET AS IN PREVIOUS COLUMN; ALKALI DISCONTINUED

Chart 2.—Curves showing the ineffectiveness of an iron-rich diet on the formation of hemoglobin in patient 2 while he was undergoing alkaline therapy and the satisfactory response after the withdrawal of alkalis.

significantly except in one patient (chart 2), in whom there was a rise in the number of red blood cells from 2,000,000 to 2,800,000 per cubic

millimeter. This reaction on the part of the bone marrow may be interpreted to indicate a decided depletion in the reserves of the substances necessary for the synthesis of hemoglobin and also, except in one patient, a lack of stroma-building material available for the production of erythrocytes.

EFFECT OF DIETARY IRON DURING ALKALINIZATION

In the second period of study the administration of alkaline powders was continued, but the diet was supplemented by foods containing iron. Sherman [4] stated that the daily requirement of iron is from 12 to 15 mg. Mettier, Kellogg and Rinehart [5] have shown that the daily administration of a meal predigested with pepsin and hydrochloric acid and containing that amount of iron causes a rapid and satisfactory increase in concentration of hemoglobin in patients with idiopathic hypochromic

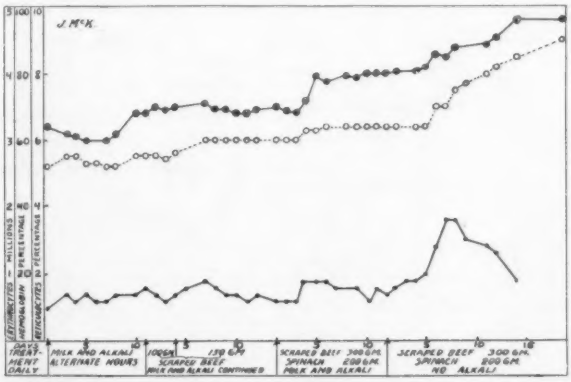
J. M°K.
MILK AND ALKALI ALTERNATE HOURS
IRON
SCRAPED BEEF MILK AND ALKALI CONTINUED
SCRAPED BEEF SPINACH MILK AND ALKALI
SCRAPED BEEF SPINACH NO ALKALI

Chart 3.—Curves showing the relative ineffectiveness of an iron-rich diet on the formation of blood in patient 3 while he was on an alkaline regimen and the satisfactory response after the withdrawal of alkalis.

anemia. Accordingly, cooked eggs, spinach and scraped beef, containing from 12 to 15 mg. of iron, were given daily. Vitamin C was provided by the ingestion of small amounts of orange juice.

The addition of this diet to the alkaline regimen was not followed by an appreciable increase in production of hemoglobin. In one patient

4. Sherman, H. C.: Chemistry of Food and Nutrition, ed. 3, New York, The Macmillan Company, 1926, p. 340.

5. Mettier, S. R.; Kellogg, F., and Rinehart, J. F.: Chronic Idiopathic Hypochromic Anemia: Etiologic Relationship of Achlorhydria to the Anemia, with Special Reference to the Effect of Large Doses of Iron, Organic (Dietary) Iron and of Predigested Food upon Formation of Erythrocytes, Am. J. M. Sc. **186**:694 (Nov.) 1933.

(chart 3) there was a rise in the concentration of hemoglobin from 55 to 60 per cent, and after the diet had been increased twofold, a rise from 60 to 64 per cent. (These slight increases are in decided contrast to the subsequent changes in the concentration of hemoglobin in the same patient.)

Definite increases in the number of erythrocytes occurred in all patients, although three (charts 1, 3 and 4) had previously shown no increase. This suggested that material necessary for the formation of stroma or for the maturation of erythrocytes was now being absorbed from the foods which had been added to the diet.

In order to determine whether or not alkalinization had unfavorably influenced the utilization of iron derived from food, the use of the powders was stopped, but the diet rich in iron was continued.

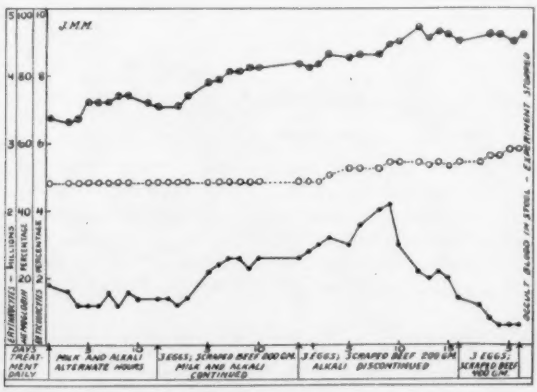
J.M.M.
DAYS UNDER TREATMENT
MILK AND ALKALI ALTERNATE HOURS
3 EGGS; 3 CANNED BEEF 200 GM. MILK AND ALKALI CONTINUED
3 EGGS; 3 SCRAPED BEEF 200 GM. ALKALI DISCONTINUED
3 EGGS; 3 SCRAPED BEEF 400 GM.
OCCULT BLOOD IN STOOL - EXPERIMENT STOPPED

Chart 4.—Curves showing the ineffectiveness of an iron-rich diet on the formation of hemoglobin in patient 4 during alkaline therapy and the slight response after the withdrawal of alkalis.

EFFECT OF DIETARY IRON WITHOUT ALKALINIZATION

Beginning on about the fourth to the sixth day after this change in therapy there was a rise in hemoglobin concentration in all four patients. For a period of from twenty to thirty days previously it had been 40, 32, 64 and 48 per cent, respectively, whereas twenty days after the change it had increased to 51, 56, 90 and 58 per cent. The increase in two patients (charts 2 and 3) was in excess of 1 per cent a day, which represents a satisfactory rate and one comparable to that produced by adequate iron therapy.[6] In one patient (chart 4) the experiment was

6. Heath, C. W.: Oral Administration of Iron in Hypochromic Anemia, Arch. Int. Med. **51**:459 (March) 1933.

stopped because of the recurrence of bleeding. In the fourth (chart 1) the substitution of 90 Gm. of mucin for the alkaline powders, with consequent partial neutralization of gastric acidity, may have modified the utilization of the dietary iron. The subsequent ingestion of iron and ammonium citrates (U.S.P., 6 Gm. daily) by the third and fourth patients induced a rapid rise in the hemoglobin content.

Coincident with the increase in hemoglobin there was a rise in the percentage of reticulocytes, which was marked in two patients (charts 1 and 3), and a further increase in the number of erythrocytes. Thus the response of the bone marrow to the withdrawal of alkaline therapy resembled qualitatively in each patient and quantitatively in two patients the response which is produced by the ingestion of large doses of inorganic iron. This fact becomes more striking when one considers the relatively small amounts of iron present in the diet administered.

COMMENT

The data obtained from the examination of the blood of four men with anemia secondary to prolonged loss of blood from a peptic ulcer serve to illustrate the changes which may take place in the formation of blood as a result of the administration of an iron-rich diet, first, while the upper part of the gastro-intestinal tract is made alkaline by a modified Sippy regimen and, second, after the alkaline therapy is discontinued. It was demonstrated that an iron-rich diet had practically no effect on the formation of hemoglobin during the period of alkalinization but that after the administration of alkalis was stopped it had a marked effect, comparable to that produced by adequate therapy with inorganic iron.

Apparently, therefore, alkaline therapy interferes with the utilization of dietary iron. Alkalinization of the upper part of the gastro-intestinal tract depresses peptic digestion and alters the p_H of this section of the intestinal tract. Both effects interfere with the digestion and the assimilation of iron in the food and explain the lack of formation of hemoglobin during the period of alkaline therapy.

This state of impaired utilization of iron for the formation of blood resembles closely that existing in patients with idiopathic hypochromic anemia. Such patients have been shown [5] to be suffering from an iron deficiency anemia wherein gastric dysfunction leads to failure in utilization of dietary iron. Thus the altered formation of hemoglobin seems to depend on the same mechanism in patients with chronic idiopathic hypochromic anemia and in the patients here discussed, in whom digestion and the p_H of the upper part of the gastro-intestinal tract were artificially altered by alkaline therapy.

Hence the present observations reemphasize the importance of the rôle of normal gastric acidity in the utilization of dietary iron for the formation of hemoglobin. In patients under alkaline treatment for peptic ulcer complicated by iron deficiency anemia, the anemia will not become less until alkalinization is discontinued, so as to allow utilization of dietary iron, or until large doses of inorganic iron are administered. From a practical standpoint, the latter treatment is the method of choice, as the foods containing large amounts of iron are those which favor a recurrence of peptic ulcer, especially in the absence of alkaline therapy.

SUMMARY AND CONCLUSIONS

Data are presented on the influence of alkalinization of the gastrointestinal tract, as carried out with a modified Sippy regimen, on the regeneration of blood by dietary iron in a group of four men with anemia following prolonged bleeding from a peptic ulcer.

The response of the bone marrow, as determined by the production of hemoglobin and erythrocytes, to dietary iron with alkaline therapy is compared to the response of the bone marrow to the same amounts of dietary iron after cessation of the alkaline regimen.

The bone marrow failed to respond to the ingestion of dietary iron while the patients were undergoing the alkaline therapy, but on withdrawal of the alkaline regimen an increase in concentration of hemoglobin occurred. In contrast, increases in the number of erythrocytes and reticulocytes occurred soon after the addition of the iron-rich diet to the alkaline regimen.

It is concluded that alkalinization of the upper part of the gastrointestinal tract interferes with the utilization of dietary iron for the synthesis of hemoglobin but not with the utilization of material necessary for the formation of erythrocyte stroma.

Mrs. Katherine Purviance made the blood counts for our patients.

ETIOLOGIC SIGNIFICANCE OF STREPTOCOCCI IN EPIDEMIC ENCEPHALITIS

I. INCIDENCE OF STREPTOCOCCI IN CULTURES FROM PATIENTS WITH ENCEPHALITIS IN ST. LOUIS AND FROM NORMAL CONTROLS, AND CHARACTERISTICS OF THE VARIOUS STRAINS ISOLATED

KENNETH L. BURDON, PH.D.

ERIC W. THURSTON, M.D.

PHILIP L. VARNEY, PH.D.

AND

J. BRONFENBRENNER, PH.D., D.P.H.

ST. LOUIS

The outbreak of acute epidemic encephalitis in St. Louis in the summer of 1933 offered an especially propitious opportunity to investigate the etiologic importance of streptococci in this disease as a parallel study to that being carried on with the filtrable virus by our associates. We were further stimulated to undertake this work by the presence in St. Louis of Dr. E. C. Rosenow, who was studying this same question and who was accumulating evidence similar to that advanced by him in the past indicating, in his opinion, the primary rôle of streptococci in the causation of the St. Louis form of the disease.

In view of the prominence of Rosenow's work in this field and in consideration of the fact that his results have been attained by following a special technic, our efforts were confined largely to a repetition of his studies, with as nearly as possible identical methods. We made a particular effort to learn the details of his technic and to follow it precisely. In this we had the full cooperation of Dr. Rosenow, who visited our laboratory repeatedly and gave us a complete demonstration of his procedures.

The results of this investigation are reported in two papers. In the present communication the incidence of streptococci in cultures from

---

This investigation was undertaken as a part of the general study of the etiology of encephalitis conducted under the auspices of the Metropolitan Health Council of St. Louis during the epidemic of acute encephalitis in the summer of 1933. A summary appears in Public Health Bulletin 214 of the United States Public Health Service.

From the department of bacteriology and immunology, Washington University School of Medicine.

patients with encephalitis and from normal controls and the cataphoretic velocity, agglutination reactions and general characteristics of the organisms in these cultures are discussed. In the second paper experiments with animals, designed to investigate the question of the etiologic relationship to clinical encephalitis of the several strains of streptococci studied, are described, and the conclusions drawn from the whole study are given.

REVIEW OF THE LITERATURE CONCERNING THE ETIOLOGIC RELATIONSHIP OF STREPTOCOCCI TO ENCEPHALITIS

Since the recognition of epidemic encephalitis as a distinct clinical entity by von Economo in 1917, numerous investigators have sought to discover the specific etiologic agent among the bacteria or among the filtrable viruses. Observations suggesting a bacterial causation of this disease were reported early, and a few workers, notably Rosenow, have consistently upheld the view that certain visible and cultivable microorganisms are of primary etiologic importance. On the other hand, the failure to cultivate any bacteria from human tissues in many cases and the obvious analogy with known virus diseases in respect to clinical, pathologic and epidemiologic features have led the majority of investigators to believe that the etiologic agent of epidemic encephalitis must be an ultramicroscopic virus. Unfortunately, attempts on the part of several groups of workers to isolate and identify a specific virus through inoculation of animals gave divergent and inconclusive results, particularly in the many researches in which rabbits were used as the experimental animals. This was due in part to the occurrence of spontaneous encephalitis in rabbits and in part to confusion of the hypothetic virus of encephalitis with the virus of herpes or of rabies, or with other viruses producing symptoms in rabbits.

However, well documented evidence in favor of a specific filtrable virus, distinct from the virus of herpes, as the etiologic agent of encephalitis was brought forward by McIntosh[1] in the Derby epidemic in England in 1919 as well as by Takagi,[2] who investigated the epidemic of

1. McIntosh, J.: Transmission of Experimental Encephalitis Lethargica in a Series of Monkeys and Rabbits, with Notes on Spontaneous Infection in the Monkey, Brit. J. Exper. Path. **1**:257 (Oct.) 1920. McIntosh, J. A., and Turnbull, H. M.: Experimental Transmission of Encephalitis Lethargica to the Monkey, ibid. **1**:89 (April) 1920.

2. Takagi, I.: Etiology of Encephalitis Occurring Epidemically in Japan in 1924, Japan M. World **5**:147 (June) 1925; Virus of Encephalitis Japonica, Ztschr. f. Immunitätsforsch. u. exper. Therap. **47**:441, 1926.

1924 in Japan. Nevertheless, the conclusion reached by several authors [3] of recent authoritative reviews of this subject seemed to be that the true nature of the etiologic agent had not as yet been clearly established, although a filtrable virus was the most likely cause of epidemic encephalitis.

The study of the acute form of encephalitis in the St. Louis epidemic of 1933 brought definite evidence for the virus etiology. Muckenfuss, Armstrong and McCordock [4] as well as Webster and Fite [5] recovered from the brains of patients with fatal encephalitis a filtrable virus which reproduced in monkeys and in mice clinical symptoms and pathologic changes closely resembling in most of their features the picture of encephalitis in human beings. Further, they showed that this virus is specifically neutralized by the serum of convalescent or recovered patients.[6] The pathologic changes produced by the virus in mice have been described more fully by Smadel and Moore.[7] The results of these investigations seem to leave little doubt as to the primary etiologic rôle played by a specific filtrable virus in the form of epidemic encephalitis which occurred in St. Louis, and they lend weight to the view that other outbreaks of this disease may have been due to a similar, if not identical, virus.

On the other hand, the possible etiologic importance of streptococci has been repeatedly suggested since the earliest description of epidemic encephalitis as a specific disease. Von Weisner,[8] in 1917, inoculated a

---

3. (*a*) Zinsser, H.: Present State of Knowledge Regarding Epidemic Encephalitis: Thirteenth Mellon Lecture, Arch. Path. **6**:271 (Aug.) 1928. (*b*) Neal, J. B.: Present Status of the Etiology of Epidemic Encephalitis, J. A. M. A. **91**:231 (July 28) 1928. (*c*) Stern, F.: Die epidemische Encephalitis, ed. 2, Berlin, Julius Springer, 1928. (*d*) von Economo, C.: Die Encephalitis lethargica, ihre Nachkrankheiten und ihre Behandlung, Berlin, Urban & Schwarzenberg, 1929. (*e*) Levaditi, C.: Etiology of Epidemic Encephalitis: Its Relation to Herpes, Epidemic Poliomyelitis and Post-Vaccinal Encephalopathy, Arch. Neurol. & Psychiat. **22**:767 (Oct.) 1929. (*f*) Epidemic Encephalitis: Etiology, Epidemiology, Treatment; Report of a Survey by the Mathewson Commission, New York, Columbia University Press, 1929; (*g*) Second Report, 1932.

4. Muckenfuss, R. S.; Armstrong, C., and McCordock, H. A.: Encephalitis: Studies on Experimental Transmission, Pub. Health Rep. **48**:1341 (Nov. 3) 1933.

5. Webster, L. T., and Fite, G. L.: Virus Encountered in the Study of Material from Cases of Encephalitis in St. Louis and Kansas City Epidemics of 1933, Science **78**:463 (Nov. 17) 1933.

6. Webster, L. T., and Fite, G. L.: Proc. Soc. Exper. Biol. & Med. **31**:344 (Dec.) 1933. Muckenfuss, R. S.: Bull. New York Acad. Med. **10**:444 (July) 1934. Muckenfuss, R. S.; Armstrong, C., and Webster, L. T.: Etiology of the 1933 Epidemic of Encephalitis, J. A. M. A. **103**:731 (Sept. 8) 1934. Wooley, J. G., and Armstrong, C.: Pub. Health Rep. **49**:1495, 1934. Webster and Fite.[5]

7. Smadel, J. E., and Moore, E.: Am. J. Path. **10**:827, 1934.

8. von Weisner: Wien. klin. Wchnschr. **30**:933, 1917.

monkey with material from the brain of the patient in one of the first cases described by von Economo[9] and produced an acute illness after an incubation period of only a few hours, with death in two days. From the brain of this monkey he recovered a diplostreptococcus, which on subsequent inoculation into another monkey produced a somewhat similar disease. Although the acute course of the experimental infection in the monkeys was unlike the clinical picture characteristic of epidemic (lethargic) encephalitis of von Economo in human beings, von Wiesner nevertheless considered the streptococci to be the probable cause of the disease in human beings.

A considerable number of other authors have reported the isolation of streptococci from the spinal fluid, ventricular fluid or brain substance and occasionally from the blood of human patients, as well as from the brains of experimentally inoculated animals. Among the more important papers mentioning the finding of streptococci are those of Stafford,[10] Morse and Crump,[11] House,[12] Cohn and Lauber,[13] Brasher, Caldwell and Coombe,[14] Bernhardt and Simons,[15] Reichert,[16] Siegmund[17] and others.[18] In view of a certain degree of similarity in clinical and epidemiologic features between the outbreak in Japan in 1924 and that in St. Louis in 1933, it is of special interest to note that several of the Japanese investigators occasionally isolated diplococci or streptococci from their patients, as stated in the review by Kaneko and Aoki.[19]

A survey of the literature reveals that diplococci or streptococci have been encountered more frequently than any other kind of cultivable bacteria in materials from patients with encephalitis presumably containing the etiologic agent of the disease. However, isolation of these organisms directly from the human brain or spinal fluid or from animals inoculated experimentally with these materials has succeeded only occasionally and without regularity. Furthermore, in the hands of most workers, attempts to reproduce the disease in animals by the injection of cultures of streptococci isolated from these sources have led to

9. von Economo, C.: Wien. klin. Wchnschr. **30**:581, 1917.

10. Stafford, C. M.: J. Lab. & Clin. Med. **4**:691, 1919.

11. Morse, P. F., and Crump, C. S.: J. Lab. & Clin. Med. **5**:275, 1920.

12. House, W.: Epidemic (Lethargic) Encephalitis, J. A. M. A. **74**:884 (Feb. 7) 1920.

13. Cohn, W., and Lauber, I.: München. med. Wchnschr. **67**:688, 1920.

14. Brasher, C. W. J.; Caldwell, J. R., and Coombe, E. J.: Brit. M. J. **1**:733, 1919.

15. Bernhardt and Simons: Neurol. Centralbl. **38**:705, 1919.

16. Reichert: Centralbl. f. Bakt. **85**:261, 1920.

17. Siegmund: Berl. klin. Wchnschr. **57**:509, 1920.

18. Additional references will be found in the report of the Mathewson Commission on Epidemic Encephalitis[8f] and in the paper by Rosenow and Jackson.[20]

19. Kaneko and Aoki: Ergebn. d. inn. Med. u. Kinderh. **34**:342, 1928.

negative or inconclusive results. For these reasons very few authors have regarded the streptococci as the primary cause of encephalitis; the majority have considered them as secondary invaders or contaminants.

The principal evidence suggesting the primary importance of the streptococcus in the etiology of encephalitis has been brought forward in the extensive studies of Rosenow and his collaborators, and these experiments stand apart from all those before mentioned. In this work strains of green colony streptococci having apparently distinct neurotropic properties were repeatedly isolated directly from material from human beings as well as from experimentally infected animals during the study of various outbreaks of epidemic encephalitis, including the St. Louis epidemic of 1933. Furthermore, the symptoms and pathologic changes produced in rabbits by inoculation with these streptococci were identified by Rosenow with those characteristic of epidemic encephalitis in human beings. Throughout his studies Rosenow used a particular kind of culture medium (dextrose-brain broth) because of its selective effect in favoring the growth of streptococci. He also followed certain technical procedures not commonly employed by other bacteriologists and attributed his success largely to the efficiency of his methods.

Earlier Studies of Rosenow.—In an early report Rosenow [20] stated that pleomorphic diplococci or streptococci were found on microscopic examination in or near the lesions in sections of the brain and medulla from each of a group of twenty-one patients with encephalitis, whereas these organisms were absent in tissues free from pathologic changes and in sections from the brains of persons dying of other disease which he examined as controls. In several of his later communications similar findings have been reported.

Even with the use of his selective medium, however, Rosenow, like other investigators, has succeeded in the cultivation of streptococci directly from the brains or spinal fluid of only a small proportion of the patients he has studied. Furthermore, in only rare instances has he produced illness in rabbits by direct intracerebral inoculation of the material from the brain or spinal fluid from patients with encephalitis, and in all these cases the experimental disease in the rabbits was evidently due to the streptococci, which were readily cultivated from the brains of the animals after death.

The bulk of Rosenow's studies have begun with streptococci obtained, not directly from the infected tissues of the human brain, but from the nasopharynx, tonsils or similar "atria of infection." On the assumption that these areas, in patients suffering from any of the various clinical forms of epidemic encephalitis, would harbor the specific neuro-

20. Rosenow, E. C., and Jackson, G. H., Jr.: J. Infect. Dis. **32**:144, 1923.

tropic streptococci responsible for the disease, Rosenow inoculated rabbits with the original suspension of swabbings from these areas or with primary cultures in dextrose-brain broth. He found that intravenous inoculation of the original mixture of bacteria did not result constantly in localization of streptococci in the brain. However, when these suspensions, or cultures obtained from them, were inoculated intracerebrally in small doses, a culture containing only green colony streptococci was usually obtained from the brains of the animals after death, while the blood from the heart was nearly always sterile. Impressed by these findings, Rosenow concluded that inoculation of the original mixtures into the brain of the living animal served like a culture on an agar plate for the separation of neurotropic strains of green colony streptococci.[21]

Furthermore, when the rabbits were inoculated intracerebrally with nasopharyngeal washings or with the mixed primary cultures of these secured from patients with epidemic hiccup[22] or respiratory arrhythmias[23] (conditions which he thought to have the same cause as encephalitis), spasms of the diaphragm or respiratory disturbances, respectively, developed in a certain proportion of the animals, and these symptoms were more pronounced and were observed more frequently by Rosenow in these animals than in rabbits similarly inoculated with material from other sources.

Likewise, in the several hundred rabbits inoculated by Rosenow intracerebrally with similar cultures from patients with conditions definitely diagnosed as encephalitis,[24] the symptoms in the animals were regarded as a reproduction of the lethargic, parkinsonian, myoclonic or meningeal type of encephalitis, corresponding to the form of the disease in the patients from whom the cultures were obtained. He called attention to the fact that in most of the control rabbits receiving inoculations of nasopharyngeal cultures from normal persons there also developed symptoms referable to the central nervous system, but these symptoms, as a rule, were less severe. Thus, of five hundred and nineteen rabbits inoculated with material from eighty-one patients with encephalitis, 74 per cent died, while of one hundred and six rabbits receiving material from normal persons, only 23 per cent died. In both groups of animals most of the deaths occurred within three days after the inoculation.

21. Rosenow, E. C.: J. Infect. Dis. **32**:41 and 72, 1923.

22. Rosenow, E. C.: Diaphragmatic Spasms in Animals Produced with a Streptococcus from Epidemic Hiccup, J. A. M. A. **76**:1745 (June 18) 1921. Rosenow.[21]

23. Rosenow, E. C.: Experiments on the Etiology of Respiratory Arrhythmia Following Epidemic Encephalitis, Arch. Neurol. & Psychiat. **11**:155 (Feb.) 1924.

24. Rosenow, E. C.: (*a*) Etiology of Encephalitis, J. A. M. A. **79**: 443 (Aug. 5) 1922; (*b*) J. Infect. Dis. **34**: 329, 1924.

With some of the cultures of streptococci recovered from the brains of the rabbits after the original inoculation of the unpurified primary cultures, it was possible to reproduce in a series of rabbits practically the same train of symptoms shown by the first animal, but more often the character of the symptoms gradually changed on repeated passage in animals, as a result, according to Rosenow, of a change in the "specific localizing power" of the micro-organism.[25] This change was especially marked in prolonged cultivation on ordinary mediums but could be somewhat minimized if the cultures were transferred in dextrose-brain broth at frequent intervals (from 4 to 6 times each twenty-four hours).

The pathologic changes in the inoculated rabbits were found to vary considerably according to the rapidity with which death followed the inoculation. Usually, in animals that died a week or longer after the injection, the gross appearance of the brain was normal. In the animals dying earlier there were visible a marked congestion of cerebral vessels, "occasional slight general clouding of the meninges, localized infiltration of the pia over the anterior aspect of the midbrain, pons and medulla, associated with slightly or moderately turbid cerebrospinal fluid, small subpial hemorrhages, especially of the medulla and pons, more rarely of the cord and cerebral cortex, rarely a lesion at the point of inoculation, and a variable degree of hemorrhagic edema of the lungs and cloudy swelling of other viscera. Suppurative meningitis, when present, was almost always due to some organism (usually hemolytic streptococcus or staphylococcus) other than the green-producing streptococcus." [26]

Microscopic examination of the brains of animals dying in five days or earlier (i. e., the great majority of the rabbits) showed "leukocytic and round cell infiltration of the pia," focal hemorrhages in the brain and the medulla, often perivascular, associated with a variable degree of cellular infiltration and areas of similar infiltration without hemorrhage. It appears that a considerable proportion of the animals showed a frank purulent meningitis in addition to any other lesions. This meningeal involvement was noted by Rosenow particularly in those animals inoculated with a strain of streptococcus which had gone through a series of rapid passages in animals. In general, the early reaction (in animals dying before the sixth day), which consisted of "a variable degree of leukocytic and round cell infiltration in the meninges and elsewhere," did not differ from the response observed in rabbits inoculated with material obtained from normal persons. However, in animals surviving six days or more, round cells rather than polymorphonuclear

25. Rosenow, E. C.: J. Infect. Dis. **33**:531, 1923.

26. Rosenow,[24b] p. 367.

leukocytes tended to predominate, especially in perivascular infiltrations in the depths of the brain. This "characteristic round cell infiltration" was usually lacking in rabbits inoculated with material from normal persons.[27]

As to the characteristics of the streptococci isolated from the patients with encephalitis, Rosenow described them as "somewhat peculiar" pleomorphic organisms, usually producing green colonies on blood agar. A few strains were found to be soluble in bile, but the majority would be classified as Streptococcus viridans. The variable morphology of the organisms as seen in tissues and in cultures was stressed, and this pleomorphism was thought to be correlated with the apparent filtrability of certain strains. This property of filtrability was regarded by Rosenow as definitely established, since filtrates of cultures and of other materials sometimes produced the usual symptoms when inoculated intracerebrally into rabbits. However, he stated that in cases in which filtrates were capable of eliciting symptoms of any kind streptococci of normal morphology could be cultivated either from the filtrate itself or at least from the brain of the rabbit after death.[28] As previously stated, the streptococci from patients with encephalitis exhibited a marked tendency to localize in the nerve tissues, and some experiments indicated to Rosenow that this localization might be determined, in part at least, by the production of a "specific poison." [29] Since these streptococci appeared to resemble those found in the normal human respiratory tract, Rosenow conceived their specific neurotropic properties to be temporarily acquired as "a phase, perhaps, in the life cycle of the streptococcic group of organisms." [30]

More recently, Rosenow reported that the specific streptococci of encephalitis could, as a rule, be differentiated from strains occurring in normal throats on the basis of their average cataphoretic velocity.[31] As a result of a great number of determinations of the cataphoretic velocity of the organisms in primary, unpurified dextrose-brain broth cultures from the nasopharynges of patients with encephalitis and of other persons, and of the velocities shown by cultures of streptococci recovered from the brains of inoculated rabbits after death, Rosenow concluded that the average cataphoretic velocity of streptococci of a

27. Rosenow,[24b] p. 368.

28. Rosenow,[24b] p. 380.

29. Rosenow, E. C.: Localization in Animals of Streptococcus from Cases of Epidemic Hiccup, Encephalitis, Spasmodic Torticollis and Chorea, Arch. Neurol. & Psychiat. **19**:424 (March) 1928.

30. Rosenow, E. C.: Specificity of Streptococci in the Etiology of Diseases of the Nervous System, J. A. M. A. **82**:449 (Feb. 9) 1924.

31. Rosenow, E. C., and Jensen, L. B.: J. Infect. Dis. **52**:167, 1933.

particular strain is a characteristic definitely correlated with the source and elective localizing capacity of that strain.

Thus, under the set experimental conditions of observation he found that both the primary and the passage cultures of streptococci originating from patients with encephalitis required on the average about 4 seconds to traverse the standard distance of 50 microns in the electric field.[31] This same range of cataphoretic velocities was shown by other "neurotrophic" strains of streptococci recovered by Rosenow, from patients with other diseases of the nervous system, such as those obtained from patients with poliomyelitis.[32] In contrast, streptococci from the throats of normal persons had a higher cataphoretic velocity, showing under the same experimental conditions a cataphoretic time of only about 3 seconds. On the other hand, strains of streptococci originating from persons afflicted with diseases other than those involving the nervous system showed an average cataphoretic velocity different from that of organisms from either normal subjects or persons with encephalitis. Those from patients with influenza, for example, had an average cataphoretic time of from 4.5 to 5 seconds.[33] Repeated determinations showed, however, that strains which had a particular average velocity when originally secured did not always maintain this characteristic unchanged on further artificial cultivation or after passage in animals.

Rosenow stated further that streptococci originating from patients with encephalitis differed from those derived from normal persons in their immunologic properties also. Antistreptococcus serums prepared by hyperimmunizing horses with a mixture of strains of streptococci obtained by Rosenow in his earlier work with encephalitis (1923) and with poliomyelitis were found to agglutinate the streptococci isolated during subsequent study of various outbreaks of encephalitis, and this agglutination reaction was regarded as specific for the "encephalitis" streptococcus. He stated: "When agglutination of a particular strain was more marked, and when it occurred in higher dilutions in the encephalitis and poliomyelitis hyperimmune serums than in the type pneumococcus serums, immune streptococcus serum from influenza, and normal horse serum, it was considered specific agglutination" [34] He noted that the agglutinability of different strains from patients with encephalitis varied greatly, and only rarely was the titer high.

Though agglutination tests with the serums obtained from patients convalescing from encephalitis during studies of various outbreaks of the disease never gave consistent results, their agglutinating power for typical strains of streptococci producing encephalitis was weak at best,

32. Rosenow, E. C.: J. Infect. Dis. **50**:377, 1932.
33. Rosenow, E. C.: J. Infect. Dis. **54**:91, 1934.
34. Rosenow,[24b] p. 385.

Rosenow nevertheless considered the results as indicative of a definite, though feeble, specific reactivity.[30]

He found, furthermore, that his encephalitis antistreptococcus serum had some protective power for rabbits inoculated with streptococci isolated from patients with encephalitis, and consequently this serum was early recommended by Rosenow for use in treatment of human patients with encephalitis.[35]

Reports of Other Investigators.—Observations which might be regarded as offering direct support of Rosenow's views were made by Evans and Freeman in 1926. With nasal washings and with cultures of streptococci recovered from the blood and the mesencephalon of a patient dying of encephalitis these authors produced a rapidly fatal meningo-encephalitis in rabbits and in monkeys. Filtrates of cultures and of the emulsions of brains of human beings and of animals proved harmless; but when such filtrates were planted in a meat medium, streptococci could later be recovered from this medium. These findings indicated to the authors that the streptococci must have existed in filtrable form in the original material from the brain. In some of the cultures inoculated with emulsions of human brain they found not only streptococci, but also diphtheroids and spore-forming bacilli. They suggested that these bacteria, as well as the streptococci, were only the visible forms of an invisible, filtrable virus of encephalitis.[36] (Evans has more recently described in some detail her views on this "metamorphosis" of streptococci into spore-bearing rods and further into filtrable forms [37]). Freeman [38] cultivated streptococci from several other patients with encephalitis, and Evans [39] cultured these organisms from six samples of material containing the virus of herpes.

On the other hand, Olitsky and Long, [40] using Evans' technic, were unable to find any connection between the virus of herpes and streptococci, and Tang and Ruiz Castaneda,[41] after a similar study, concluded that visible organisms, including streptococci, which may occasionally be cultivated from samples of viruses producing encephalitis in rabbits are secondary invaders or accidental contaminants and have nothing to do with the viruses themselves. The same conclusion was reached by

35. Rosenow, E. C.: Specific Serum Treatment of Epidemic (Lethargic) Encephalitis: Further Results, J. A. M. A. **80**:1583 (June 2) 1923.

36. Evans, A. C., and Freeman, W.: Pub. Health Rep. **41**:1095, 1926.

37. Evans, A. C.: Pub. Health Rep. **47**:1723, 1932.

38. Freeman, W.: Chronic Epidemic Encephalitis, J. A. M. A. **87**:1601 (Nov. 13) 1926; Encephalitis with Tumor of the Brain, Arch. Neurol. & Psychiat. **18**: 433 (Sept.) 1927; J. Nerv. & Ment. Dis. **65**:171, 1927.

39. Evans, A. C.: Pub. Health Rep. **42**:171, 1927.

40. Olitsky, P. K., and Long, P. H.: J. Exper. Med. **48**:199, 1928.

41. Tang, F. F., and Ruiz Castaneda, M.: J. Bact. **16**:431, 1928.

McKinley and Douglass [42] in connection with their studies of herpes encephalitis in cebus monkeys.

McKinley [43] stated that by following Rosenow's technic in all details he succeeded in producing a fatal meningo-encephalitis in rabbits by intracerebral inoculation of nasopharyngeal cultures from a high proportion (80 per cent) of a group of healthy persons in Puerto Rico. Furthermore, in his opinion, the symptoms and pathologic changes in these rabbits were the same as those in rabbits similarly inoculated by Rosenow with cultures from patients with encephalitis and demonstrated to him in Rosenow's laboratory. So far as we are aware, this is the only study of encephalitis aside from our own which was conducted exactly according to Rosenow's technic.

Rosenow's Findings in St. Louis.—Employing the same methods of experimental study and the same technical procedures which he had followed in the past, Rosenow investigated cases of encephalitis in St. Louis during the height of the epidemic of 1933. His principal findings [44] were in all essentials similar to those obtained by him in the earlier studies reviewed in this paper. He demonstrated, either by direct microscopic examination or by culture in dextrose-brain broth, the presence of streptococci in the specimens of spinal fluid, blood and glycerinated brain from several patients with encephalitis in St. Louis, and he stated that all the strains isolated from these sources exhibited a characteristic velocity in the electric field and were virulent when inoculated into rabbits. The organisms in 81 per cent of the primary dextrose-brain broth cultures of material from the nasopharynx of sixty-four persons suffering from acute encephalitis were found to have "mainly neurotropic cataphoretic velocity" (i. e., a cataphoretic time of from 3.5 to 4 seconds), whereas only 52 per cent of the cultures from one hundred and forty-nine well persons or from persons with diseases other than encephalitis residing in the epidemic zone and 28 per cent of an equal number of cultures from persons without encephalitis living remote from the epidemic showed a similar range of cataphoretic velocities.

Intracerebral inoculation into a large series of rabbits of streptococci from primary brain broth cultures of material from the nasopharynx or from the spinal fluid of the patients with encephalitis, or of purified cultures of streptococci from these sources, produced in the rabbits an acute and usually rapidly fatal illness, and in Rosenow's

42. McKinley, E. B., and Douglass, M.: J. Infect. Dis. **47**:511, 1930.

43. McKinley, E. B.: Proc. Soc. Exper. Biol. & Med. **27**:436, 1930.

44. Rosenow, E. C.: Proc. Staff Meet., Mayo Clin. **8**:559 (Sept. 13) 1933; Weekly Bull. St. Louis M. Soc. **28**:69 (Oct. 13) 1933; Proc. Soc. Exper. Biol. & Med. **31**:785 (Nov.) 1933.

opinion these animals showed "the more important clinical and pathologic manifestations" of encephalitis as seen in the human patients in St. Louis. On the other hand, cultures from the nasopharynges of normal persons, inoculated in the same way, caused symptoms and death in a smaller proportion of rabbits, and the lesions were considered to be "less marked."

Rosenow's "encephalitis antistreptococcus serum" was found to agglutinate "markedly and in high dilution" most of the strains of streptococci obtained by him from patients with encephalitis and also partially protected rabbits when mixed with the streptococci before inoculation. It was stated that the serum of convalescent patients with encephalitis in St. Louis agglutinated specifically and slowed the cataphoresis of the "more sensitive" strains of streptococci isolated from patients with typical manifestations.

METHODS

As indicated, we endeavored to follow as closely as possible the technical procedures described and personally demonstrated to us by Dr. Rosenow. The methods employed in the work reported in this communication are outlined in the following paragraphs.

Selective Medium.—Dextrose-brain broth medium was prepared by placing in tall, narrow tubes (20 cm. by 1.5 cm.) small pieces of fresh washed calf brains to a depth of about 2½ inches (6.3 cm.) and adding dextrose broth in sufficient amount to make the tube about three-fourths full. The broth was prepared with 10 Gm. of Bacto peptone, 5 Gm. of sodium chloride, 2 Gm. of chemically pure dextrose and 10 cc. of Andrade's indicator per liter and adjusted to p_H 7.4. A small amount of calcium carbonate (powder) was added to each of the tubes before they were placed in the autoclave for twenty minutes at a pressure of 15 pounds (6,803 Gm.).

Cultures from the Nasopharynx.—Material for these cultures was secured by passing a small sterile cotton swab on the end of an aluminum wire, bent at a suitable angle, over the nasopharynx while the throat was illuminated with a small flash-light to which the tongue depressor was attached. By this method satisfactory swabbings from an area limited strictly to the nasopharyngeal region were secured with the greatest ease. The organisms adhering to the swab were thoroughly emulsified in 2 cc. of warm, sterile Locke's solution containing 0.2 per cent gelatin, and the resulting emulsion together with the swab was placed for one hour in the incubator. The emulsion was then inoculated into a tube of warm dextrose-brain broth and also streaked on two warm hormone rabbit blood agar plates by means of the original swab. At first additional blood agar plates were streaked and incubated anaerobically,[45] but this was soon abandoned, since no additional information was gained thereby.

Smears stained by Gram's method were prepared from the twelve to twenty-four hour dextrose-brain cultures, and careful records were kept of the morphology of the organisms. The primary blood agar plates were examined; the amount and character of the growth were recorded, and smears were usually made from several representative colonies.

45. Varney, P. L.: J. Lab. & Clin. Med. **11**:1183, 1926.

Determinations of Cataphoretic Velocity.—In order to learn the details of the procedure and apparatus used by Dr. Rosenow for the determination of cataphoretic velocity, one of us visited his laboratory at Rochester, Minn. There, the method of making determinations was practiced until in a series of parallel tests on a number of different cultures quantitative results were regularly obtained agreeing within less than 1 per cent with those of the worker charged with these determinations in Dr. Rosenow's laboratory. An apparatus similar in every essential respect to that employed by Rosenow [32] was set up in our laboratory.

Material for the tests was secured by removing 2 or 3 cc. of the liquid portion of the dextrose-brain broth cultures into chemically clean test tubes, numbered serially. These tubes were centrifugated at 1,400 revolutions per minute for ten minutes; the supernatant broth was then thoroughly drained off, and the sedimented organisms were suspended in approximately 17 cc. of distilled water. Readings on these suspensions were usually made at once, and in no case was the examination delayed for more than two hours. Each suspension in distilled water, after a thorough shaking, was introduced into a Northrop-Kunitz-Mudd cataphoresis apparatus, and the time required (in seconds and quarter-seconds) for each of from twenty to twenty-five organisms in the suspension to traverse the unit distance of 50 microns was determined by a stop-watch.[46]

The accuracy of the determinations was controlled in several ways. The drop in voltage between the platinum electrodes was determined by direct readings just before and just after performance of the tests on a group of cultures and was found to vary in the course of the determinations not more than $\pm$ 1.5 per cent. This variation was considered as a limit of error of the method. At different times between individual determinations the cataphoretic time of the particles of Lloyd's reagent was measured, and the readings on the cultures were not considered valid unless those on Lloyd's reagent showed an average time of approximately 4.5 seconds. All the measurements of cataphoretic velocity were made by the same person, who at the time had no knowledge of the source of the cultures. In nearly every group of cultures tested at one time, one or more samples were submitted for examination in duplicate as a further means of checking the accuracy of the readings.

INCIDENCE OF STREPTOCOCCI IN CULTURES FROM PATIENTS WITH ENCEPHALITIS AND FROM NORMAL CONTROLS

Cultures from the Brain, Spinal Fluid and Blood of Patients with Encephalitis.—We did not undertake a systematic bacteriologic study of specimens of brain, spinal fluid or blood, but a few samples of these

46. The average of these readings on a particular culture gives the average cataphoretic time of the organisms in that culture. The average cataphoretic velocity is expressed in terms of microns per second, volts per centimeter, according to the formula:

$$\text{Cataphoretic velocity} = \frac{\text{standard distance traversed (50 microns)}}{\text{time in seconds}} \times \frac{\text{distance between platinum electrodes}}{\text{total voltage drop}}.$$

Thus, in our apparatus, with the platinum electrodes 3.58 cm. apart and the voltage drop between them 29.5 volts, an organism with an average cataphoretic time of four seconds has a velocity expressed as 1.52. C.V. $= \frac{50 \times 3.58}{4 \times 29.5} = 1.52$ (charts 1 and 2).

materials were cultured, most of them prior to the beginning of any experimental work. On ordinary mediums of several kinds (including cooked meat medium but not including dextrose-brain broth) cultures were made from specimens of the fresh brain and of glycerinated emulsions of brain from sixteen different patients with encephalitis. No growth appeared in any case in the mediums inoculated with the specimens of fresh brain. The glycerinated emulsions of brain, however, were found to contain a few bacteria in several cases, but these were of diverse kinds, mostly diphtheroids and staphylococci, and streptococci were observed in cultures from only two specimens, in each of which these organisms were accompanied by diphtheroids. Cultures of blood from fifteen patients with encephalitis made in ordinary infusion broth were all sterile, except one in which a large gram-positive bacillus, evidently a contamination, was found. No growth developed in cultures inoculated with specimens of spinal fluid from seventeen different patients, except in a single instance, when a mixed growth of an unidentified gram-amphophilic coccus and a gram-negative bacillus appeared.

After we began the use of Rosenow's dextrose-brain broth, we were able to make only a very few additional cultures because of the pressure of other work. Three samples of spinal fluid and two of blood from patients suffering from acute encephalitis were inoculated (a few hours after their collection) in amounts of 1 cc. or more into warm dextrose-brain broth. Only three of the five cultures ever showed any evidence of growth, and in each of these instances only a sporulating gram-positive bacillus was present.

In a single instance, however, green colony streptococci were recovered from the brain of an elderly patient who died of encephalitis. At the autopsy, conducted about twelve hours after death, ventricular fluid was collected with a pipet immediately after the skull was opened, and 1 cc. of this fluid was introduced into a tube of warm dextrose-brain broth. No growth was evident in this culture after twenty-four hours' incubation, but a transplant into another tube of brain broth medium made at that time showed turbidity in twelve hours, and a similar growth had developed by that time in the original tube. This growth was found to consist of an apparently pure culture of green colony streptococci. This particular strain was designated H Br-1, and because of its origin it was included in the studies to be described later, which otherwise dealt entirely with cultures derived from the nasopharynx.

Cultures from the Nasopharynges of Patients with Encephalitis and of Normal Persons.—Cultures of material from the nasopharynx were obtained from twenty-nine patients at the St. Louis Isolation Hospital. Twenty-one of these patients were suffering from typical acute encephalitis of from two to nine days' duration at the time the cultures were

taken. Of the remaining eight patients, five were convalescing from an acute attack of this disease which had occurred from three to six weeks previously, and three had only mild and questionable symptoms of from seven to ten days' duration.

As controls, cultures of material from the nasopharynx were made during the period of the epidemic from twelve normal persons residing in St. Louis and, in addition, from nine well persons residing at a considerable distance from the area involved in the epidemic (Washington, D. C.). The swabbings from the latter persons were secured at our request through the kindness of Dr. Leake and were brought by him to St. Louis, where they were inoculated into culture mediums in the usual way within less than twenty-four hours after they were collected.

The primary blood agar plate cultures inoculated directly with the swabbings from the nasopharynges of twenty-five of the twenty-nine patients with encephalitis (86 per cent) showed the presence of colonies of streptococci causing the alpha type of hemolysis. As may be seen in table 1, the relative number of these green colony streptococci appeared to be consistently higher in those cultures secured from acutely ill patients than in those from mildly ill or convalescent patients. Colonies of the green-producing streptococci apparently predominated in the blood agar plates from about one half of all the patients, and they occurred in almost pure culture in two instances. In addition to streptococci, many colonies of staphylococci, often of the hemolytic variety, were present in most of the blood agar plates. A smaller number of colonies of the several other kinds of bacteria normally present in the nasopharynx (especially gram-negative diplococci and diphtheroids) were also observed. Colonies of influenza bacilli were encountered in one instance only. Hemolytic streptococci were noticeably absent.

The primary cultures of material from the nasopharynx on blood agar from sixteen (76 per cent) of the twenty-one normal persons contained streptococcus colonies of the green type accompanied by a variable number of colonies of other bacteria commonly found in the nasopharynx (table 1). Among these cultures, one set of plates inoculated with material from a student in St. Louis, who was perfectly well and had not had any known contact with patients with encephalitis, yielded practically a pure growth of green-producing streptococci. These organisms appeared to be predominant in one third of the blood agar cultures from twelve normal persons in St. Louis and in an even larger proportion (56 per cent) of those made from nine healthy residents of Washington, D. C. The cultures from the latter source differed from those made from normal persons in St. Louis in that they contained a greater variety of bacteria, but the green colony streptococci were nevertheless relatively numerous.

Thus, while the number of these primary nasopharyngeal cultures observed is insufficient to permit any very definite conclusions, it appears that the blood agar cultures from the nasopharynges of the acutely ill patients with encephalitis showed a slightly greater incidence of green colony streptococci and a somewhat less varied flora than did similar cultures from normal controls. This relative uniformity of the flora was especially marked in comparison with the variety of different organisms present in the cultures from normal persons living in Washington, D. C.

The primary cultures from the nasopharynx in dextrose-brain broth, whether from the patients with encephalitis or from the normal persons, always showed, in smears, a marked predominance of gram-positive

TABLE 1.—*Relative Abundance of Streptococci in Primary Blood Agar Cultures from the Nasopharynx*

Source of Cultures	Total Cultures	Green Colony Streptococci			Staphylococci		Other Organisms	
		Many	Few	None	Many	Few	Many	Few
Acute encephalitis cases from 2 to 10 days after onset	21	13	4	4	5	12	0	15
Percentage		62	19	19	24	57	0	71
Mild encephalitis and convalescent cases	8	1	7	0	4	2	0	8
Percentage		13	87	0	50	25	0	100
Total encephalitis cases	29	25		4	23		23	
Percentage		86		14	79		79	
Normal persons in St. Louis	12	4	4	4	6	1	2	6
Percentage		33.3	33.3	33.3	50	8	17	50
Normal persons in Washington, D. C.	9	5	3	1	2	6	2	5
Percentage		56	33	11	22	67	22	56
Total normal persons	21	16		5	15		15	
Percentage		76		24	71		71	

diplococci and streptococci. Apparently owing to the selective effect of this medium, gram-negative organisms never developed, and on microscopic examination the growth appeared to consist almost entirely of gram-positive cocci, with occasional diphtheroid bacilli.

However, the cocci present in most of these primary cultures were not all streptococci by any means. Subcultures on blood agar plates showed that the growth in the brain broth cultures consisted in nearly every instance of a mixture of organisms similar to that appearing on the primary blood agar plates from the same source, except that there was usually a relatively more abundant development of the gram-positive cocci. Green colony streptococci appeared to be predominant in about the same proportion of these primary brain broth cultures from the patients with encephalitis and from the normal controls as they were in the corresponding primary blood agar plates from the same persons. In the case of the two patients with acute encephalitis and of one normal

person in St. Louis previously mentioned, the primary blood agar plates inoculated with material from the nasopharynx showed an apparently pure growth of green colony streptococci, and the brain broth cultures likewise contained the streptococci only. In all the other instances, however, a mixture of organisms developed, consisting of a variable number of staphylococci in addition to the streptococci, and often of other gram-positive cocci and diphtheroids as well.

PROPERTIES OF STREPTOCOCCI ISOLATED

Determinations of Cataphoretic Velocity.—All the primary dextrose-brain broth cultures made from the nasopharynges of patients with encephalitis and of normal persons, as well as the passage cultures of streptococci recovered at different times from inoculated animals, were tested to determine the cataphoretic velocity of the organisms. For comparison with our own strains we also tested repeatedly various subcultures of the strain used by Dr. Rosenow for demonstration in our laboratory and, in addition, five other strains isolated by him which he later sent us as examples of typical "encephalitis" streptococci. Determinations of cataphoretic velocity were frequently made on different subcultures of the same strain of streptococci, while it was being maintained by three or four transfers per day in the brain broth medium.

In general we could not discover any consistent correlation between the cataphoretic velocity and either the source or the relative virulence of the organisms when inoculated into rabbits.

Our findings on the cataphoretic velocity of the organisms in the primary cultures in dextrose-brain broth are presented graphically in chart 1. The data included in this chart were tabulated in the manner employed by Rosenow in his reports. The percentages shown are not based on the average cataphoretic time of the bacteria in individual cultures but represent the proportion of all the individual organisms in each group of cultures from a given source which had a particular cataphoretic time. We found no preponderance of organisms having a "neurotropic" velocity (i. e., a cataphoretic time of 4 seconds) in the primary cultures from patients with encephalitis. On the contrary, the group of cultures from normal persons, more than half of whom resided in a city remote from the area affected by the epidemic, had a somewhat higher proportion of organisms approaching this velocity.

Despite this failure of most of the primary cultures of material from the nasopharynges of patients with encephalitis to show the cataphoretic time, said by Rosenow to be characteristic of organisms having an elective localizing power for the central nervous system, practically all of them exhibited the expected virulence for rabbits. We were never able to distinguish any consistent differences in the effects produced in rabbits

by the inoculation of cultures containing organisms of different average cataphoretic velocity. (Description of the experiments with animals is deferred to the second paper of this series.)

The results of determinations of the cataphoretic velocity of organisms in the pure cultures of green colony streptococci obtained after animal passage by us from material from patients with encephalitis or from material from normal persons and of the six strains of "encephalitis" streptococci sent to us by Dr. Rosenow are tabulated in chart 2. In all three groups of cultures the highest percentage of organisms traversed the standard distance of 50 microns in less than from 3.5 to 4 seconds, the time neurotropic strains are expected to require, although the great majority of these cultures did produce in rabbits severe illness like that described as characteristic by Rosenow. As in

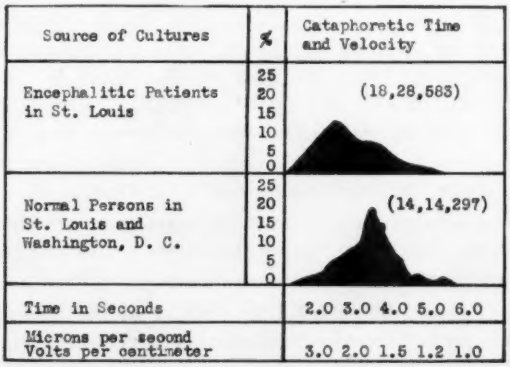

Chart 1.—Cataphoretic time and velocity of organisms in primary cultures of material from the nasopharynges of patients with encephalitis and of normal persons. The figures in parentheses give the number of strains, the number of separate cultures in each group and the number of readings on which the percentages were based.

the case of the primary cultures (chart 1) we did not observe, on the whole, any significant difference in the average cataphoretic velocity of the bacteria in cultures from different sources, and we noted nothing to indicate that a peculiar velocity is associated with the streptococci of a particular origin or of a particular degree of virulence.

This lack of correlation appeared even more striking when we considered the average cataphoretic time of the organisms in individual cultures of various origins. The figure representing this average was arrived at by averaging the observed time required for from twenty to twenty-five separate organisms of a particular culture to traverse the standard distance of 50 microns.

We found that only one of the six strains selected by Dr. Rosenow showed an average cataphoretic time approaching the "neurotropic" range of 4 seconds. This was the strain which will be referred to in subsequent experiments as Ros. 3. Even with this strain, however, the readings were not entirely consistent, for in numerous determinations made on subcultures at different times in the course of repeated passages in animals, variations in the cataphoretic time were recorded from about 2 seconds to 5 seconds. None of the other five strains ever showed an average cataphoretic time as great as 3.5 seconds. The strain used by Dr. Rosenow in our laboratory to demonstrate pathogenesis in rabbits showed by our tests averages between 2.5 and 3 seconds in repeated determinations.

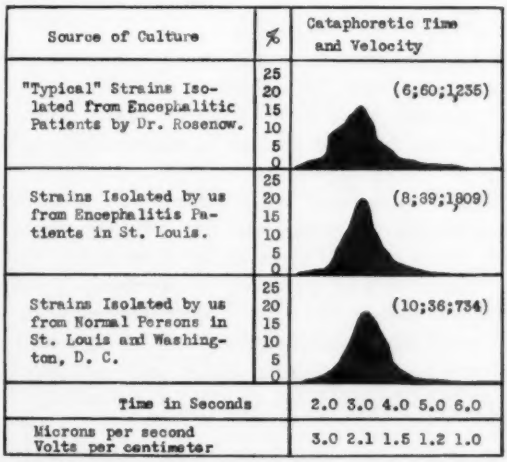

Chart 2.—Cataphoretic time and velocity of pure cultures of green colony streptococci isolated after passage in animals from patients with encephalitis and from normal persons. The figures in parentheses give the number of strains, the number of cultures in each group and the number of readings on which the percentages were based.

The strain of streptococcus previously referred to, which we isolated from the brain of a patient with encephalitis (strain H Br-1) showed an average cataphoretic time of about 3 seconds in repeated tests made both before and after passage in animals. Another culture of streptococcus, which was isolated by us originally from the brain of a rabbit inoculated intracerebrally with the primary nasopharyngeal culture from a patient severely ill with encephalitis (strain En 29) and which produced in rabbits typical symptoms, also exhibited in the majority of the many subcultures tested a cataphoretic time of only about 3 seconds.

On the other hand, cultures of the strain En 24, which were similarly virulent for rabbits, often showed a cataphoretic time as great as 4 seconds or more. Among the strains of streptococci isolated from the nasopharynges of normal persons, several showed, in repeated tests, an average cataphoretic time as great as that of any of those originating from patients with encephalitis, and most of these were also very virulent for rabbits, while a few, though exhibiting the same average velocity, were distinctly less virulent.

Thus, it can be seen that our findings on the cataphoretic velocity of streptococci from groups of cultures from different sources and on individual cultures of streptococci do not support the contention of Rosenow that a certain narrow range of cataphoretic time (around 4 seconds) is a characteristic peculiar to the virulent streptococci originating from patients with encephalitis.

Cultural Characteristics.—All the strains of streptococci isolated during this study produced the alpha type of hemolysis on blood agar plates. The colonies were mostly smooth, round disks, but rough-surfaced colonies of the types familiar in stock cultures of streptococci were plentiful in many cultures. In dextrose-brain broth and in serum broth multiplication was rapid and luxuriant, and, with the exception of a very few strains, the growth was uniform and diffuse throughout the medium. After repeated transfers in dextrose-brain broth, a few long-chained strains showed a tendency to spontaneous clumping along the sides and bottom of the tube. Morphologically the organisms appeared as small gram-positive cocci, varying somewhat in size in different cultures and occurring usually in pairs and short chains but occasionally in long chains. They appeared to be no more pleomorphic than is usual for streptococci.

None of the forty-two strains tested were found to be soluble in bile. The fermentation reactions of these strains are summarized in table 2. These reactions and the other properties mentioned appear to be those of Str. viridans.

Agglutination Reactions with Rosenow's Encephalitis Antistreptococcus Serum.—A total of fifty cultures, representing thirty-three different strains of streptococci isolated during this study, were tested for agglutination against the "encephalitis antistreptococcus serum" of Rosenow.

The results are summarized in table 3. It will be seen that all strains, including those from normal persons, were agglutinated by Rosenow's serum, but few in very high dilution. With the exception of strain H Br-1 (from the brain of a patient with encephalitis) and N 26 (from a normal throat), all cultures were agglutinated in a serum dilution at least as high as 1 : 80, and the great majority in a dilution 1 : 320. Of

the seventeen strains from patients with encephalitis only two were agglutinated in a dilution of 1:1,280 or higher. Only three of the six strains sent us by Dr. Rosenow were acted on in a dilution beyond 1:80,

TABLE 2.—*Fermentation Reactions*

Carbohydrate	Number of Strains Producing Fermentation
Dextrose	42
Lactose	41
Saccharose	42
Maltose	41
Raffinose	39
Salicin	23
Inulin	3
Mannitol	0

TABLE 3.—*Agglutination Reactions with Rosenow's Encephalitis Antistreptococcus Serum*

Source of Cultures	Strain No.	Strain Designation	Number of Cultures Tested	Number Agglutinated — Serum Dilution, 1: 20	40	80	160	320	640	1,280	2,560	5,120	10,240	Control
Patients with encephalitis	1	En 1-4	1	1	1	1	1	1	0	0	0	0	0	0
	2	En 1-7	1	1	1	1	1	1	1	0	0	0	0	0
	3	En 2-4	1	1	1	1	1	1	0	0	0	0	0	0
	4	En 4-1	1	1	1	1	1	1	0	0	0	0	0	0
	5	En 4-4	1	1	1	1	1	1	0	0	0	0	0	0
	6	En 6(Br)	3	3	3	3	3	3	3	3	1	0	0	0
	7	En 6(Bl)	2	2	2	2	2	1	1	0	0	0	0	0
	8	En 10	1	1	1	1	1	1	1	0	0	0	0	0
	9	En 14	2	2	2	2	2	1	1	0	0	0	0	0
	10	En 16	1	1	1	1	1	1	1	0	0	0	0	0
	11	En 17	1	1	1	1	1	1	1	1	1	1	1	0
	12	En 24	2	2	2	2	1	0	0	0	0	0	0	0
	13	En 28	1	1	1	1	1	0	0	0	0	0	0	0
	14	En 29	2	2	2	2	2	0	0	0	0	0	0	0
	15	En 34	1	1	1	1	1	1	1	0	0	0	0	0
	16	En 15	1	1	1	1	1	1	1	0	0	0	0	0
	17	H Br 1	1	1	0	0	0	0	0	0	0	0	0	0
Totals	17		23	23	22	22	21	15	11	4	2	1	1	0
Rosenow's cultures	1	Ros. 1	1	1	1	1	1	1	1	1	0	0	0	0
	2	Ros. 2	3	3	3	3	3	3	1	0	0	0	0	0
	3	Ros. 3	3	3	3	3	3	3	3	3	3	2	1	0
	4	Ros. 4	2	2	2	2	0	0	0	0	0	0	0	0
	5	Ros. 7	2	2	2	2	0	0	0	0	0	0	0	0
	6	302	1	1	1	1	0	0	0	0	0	0	0	0
Totals	6		12	12	12	12	7	7	5	4	3	2	1	0
Normal persons	1	N 1-7	1	1	1	1	0	0	0	0	0	0	0	0
	2	N 1-8	1	1	1	1	0	0	0	0	0	0	0	0
	3	N 1 Br	1	1	1	1	0	0	0	0	0	0	0	0
	4	N 10	1	1	1	1	1	0	0	0	0	0	0	0
	5	N 18	4	4	4	4	3	2	2	2	2	2	1	0
	6	N 19	1	1	1	1	1	1	0	0	0	0	0	0
	7	N 22	1	1	1	1	1	0	0	0	0	0	0	0
	8	N 23	1	1	1	1	1	1	1	0	0	0	0	0
	9	N 25	3	3	3	3	0	0	0	0	0	0	0	0
	10	N 26	1	1	0	0	0	0	0	0	0	0	0	0
Totals	10		15	15	14	14	7	4	3	2	2	2	1	0

and only one (Ros. 3) in a dilution beyond 1:1,280. Among the ten strains from normal throats one (N 18) was as strongly agglutinated as any of the other cultures (1:10,240 dilution). Aside from this strain, however, the organisms from normal persons were somewhat less often

agglutinated in the higher dilutions than the streptococci from patients with encephalitis. At the 1 : 640 dilution, for example, eleven of twenty-three cultures from persons with encephalitis (48 per cent), were clumped, but only three of fifteen cultures from normal persons (20 per cent) were agglutinated. The difference was obviously slight, however, and it is clear that individual strains varied greatly in agglutinability without regard to their source.

SUMMARY AND COMMENT

As a background for the present study a review of the literature bearing on the relationship of streptococci to the etiology of epidemic encephalitis is presented, from which it is clear that the experimental evidence in support of the view that streptococci play the primary rôle in the causation of this disease is to be found almost entirely in the work of Rosenow. In this and in the second communication of this series the results of an independent investigation of this question carried out during the St. Louis epidemic are reported. Throughout the work the special technical procedures used by Rosenow were followed in every detail.

The majority of cultures in ordinary mediums made from the brain tissue, blood or spinal fluid from a group of patients with encephalitis yielded no growth, while in the remaining cases bacteria of diverse kinds, and only rarely streptococci, were encountered. This failure to cultivate streptococci consistently on ordinary mediums from these sources is quite in line with the experience of other workers who have inoculated material of the same kind from patients with epidemic encephalitis without result. A few additional samples of spinal fluid cultured in Rosenow's medium (dextrose-brain broth) also failed to show the presence of streptococci. However, in the only instance in which we had the opportunity to inoculate ventricular fluid from a patient with encephalitis directly into dextrose-brain broth, a pure growth of green colony streptococci developed. After a considerable experience in its use we do not hesitate to agree with Rosenow that the brain broth medium is an unusually favorable one for the cultivation of streptococci from any source. Its wider employment by others would undoubtedly result, as in Rosenow's hands, in the more frequent demonstration of the presence of streptococci in various materials in which they may not be detected by the use of ordinary laboratory mediums.

Blood agar plate cultures from the nasopharynges of patients with encephalitis and of normal persons residing in the epidemic area as well as elsewhere seemed to indicate that there was a definite tendency for green colony streptococci to predominate in the nasopharyngeal flora of the patients acutely ill with encephalitis in St. Louis. In several cases

these organisms occurred either alone or mixed only with staphylococci. However, the cultures from normal persons showed in many instances a similar predominance of streptococci, so that on the whole the nasopharyngeal flora of the patients affected by the epidemic can hardly be regarded as distinctive.

The various strains of streptococci isolated appeared to have no unusual morphologic or cultural properties and would all be placed in the class generally designated as Str. viridans. In agglutination reactions with Rosenow's "encephalitis antistreptococcus serum" the strains originating from patients with encephalitis were agglutinated somewhat more often in the higher dilutions than those obtained from normal persons, but all the strains were agglutinated in some degree and individual strains varied greatly in agglutinability irrespective of their source.

Although our measurements of cataphoretic velocity were carefully performed, the same procedures as those employed in Rosenow's laboratory being followed, we did not confirm his findings. We could not discover any consistent correlation between the cataphoretic velocity of the streptococci and their source or their relative virulence for rabbits.

The lack of agreement between our findings and the published data of Rosenow might conceivably be due in part to differences between the medium employed in his laboratory and that used in ours. Only a limited attempt to check this point was made. Early in the course of the study we asked Dr. Rosenow to test the cataphoretic velocity of certain cultures grown in dextrose-brain broth prepared in our laboratory and the velocity of the same cultures when cultivated in parallel in his own brain broth medium. In a personal communication Dr. Rosenow reported that in three of six of these cultures the readings of cataphoretic velocity "paralleled quite accurately in the two mediums." In the remaining cultures he found a greater scattering of the range of velocities, and the organisms appeared to him to be more pleomorphic in our medium than in his own. However, the extent of variation was well within the range of that often observed and reported by Rosenow [47] in different subcultures of the same strains in the same medium.

From our admittedly limited experience we judge that there are two factors not mentioned by Rosenow which appear to have considerable influence on the results of determinations of cataphoretic velocity on cultures of the kind under discussion. These are (1) the presence of bacteria other than streptococci in most of the primary cultures and (2) the tendency of some but not all strains of streptococci to form relatively long chains when subcultured repeatedly, at intervals of a few hours (according to Rosenow's technic), in dextrose-brain broth.

47. Rosenow.[32, 33]

With respect to readings of cataphoretic velocity on the primary dextrose-brain broth cultures from the nasopharynx, the fact that these cultures almost always contain a mixture of organisms does not seem to have been given sufficient consideration. Unless one is willing to assume that every organism in these cultures is a form of pleomorphic streptococcus, it must be realized that many of the individual bacteria for which the cataphoretic time is being measured may not be streptococci at all. In consideration of this point, we believe that, in general, determinations of cataphoretic velocity on such unpurified primary cultures from the nasopharynx are of limited significance. Of course, since these cultures usually contain mainly streptococci, the greater the quantity of data the less weight this objection would have.

On repeated determinations of the cataphoretic velocity of the pure streptococci in different subcultures of the same strain at different times we noted that usually a gradual reduction in the average velocity (i. e., an increase in the cataphoretic time) occurred as the subcultures were carried through the routine, often repeated (from 4 to 6 times per day) transfers in the brain medium. With some strains the average velocity became markedly slower after several transplants, whereas with other strains the change was slight. In our experience the strains of streptococci which most frequently showed a cataphoretic time approaching an average of 4 seconds or more were the same strains that most regularly developed especially long chains after many frequently repeated transfers in dextrose-brain broth. We observed on several occasions that if one makes the determination of cataphoretic velocity in the routine way on a suspension of one of these cultures containing many long chains without attempting to avoid the formation of chains, the average cataphoretic time of the culture is always high (5 or 6 seconds or more), whereas if in making the readings one takes especial effort to avoid timing of the chained elements, the same suspension may give an average of only about 3 seconds or less. Since the routine procedure does not afford any adequate control over this factor, it seems doubtful whether figures on the cataphoretic velocity of streptococci can be strictly accurate.

STUDIES OF THE MECHANISM OF CIRCULATORY INSUFFICIENCY IN RAYNAUD'S DISEASE IN ASSOCIATION WITH SCLERODACTYLIA

MYRON PRINZMETAL, M.D.*
LOS ANGELES

Sclerodactylia and scleroderma are often associated with Raynaud's disease. Most frequently the changes in the skin occur after the vasospastic syndrome has been present for some time. Sclerodactylia occasionally occurs without pathologic arterial spasm and in some cases may precede the attacks of local asphyxia of the fingers. Occasionally the changes in the skin and the vasospastic attacks in the fingers begin simultaneously. Raynaud [1] observed the association of these closely related conditions and accurately described sclerodactylia in some of his case reports (cases 8, 11 and 15). [1a]

The skin and subcutaneous tissues in sclerodactylia are fibrotic, hard and inelastic. In severe forms the fibrosis may be so marked that motion of the fingers becomes impossible. The nails become deformed; the articulations are destroyed, and the bones, especially the terminal phalanges, are atrophied. The skin is stretched and pale, and the creases present in all normal skin are obliterated. The fingers become short, inert, tapering stumps, as a result of repeated attacks of gangrene.

When sclerodactylia is superimposed on Raynaud's disease, the ischemic process becomes greatly intensified, and attacks of gangrene repeatedly occur. Therapeutic measures, which have been reported to be helpful in cases of uncomplicated Raynaud's disease, are of no avail if sclerodactylia is present.[2]

It is my purpose in this paper to report the study of some aspects of the circulation in sclerodactylia in an effort to discover the cause of

---

* National Research Council Fellow in Medicine.

From the Thorndike Memorial Laboratory, Second and Fourth Medical Services (Harvard), the Boston City Hospital; the Department of Medicine, the Harvard University Medical School, and the Department of Medicine, the University of California Medical School, San Francisco.

1. Raynaud, A. G. M.: (*a*) De l'asphyxie locale et de la gangrène symétrique des extrémites, Paris, Rignoux, 1862; translation by T. Barlow: On Local Asphyxia and Symmetrical Gangrene of the Extremities, Selected Monographs, London, The New Sydenham Society, 1888, vol. 121, p. 1; (*b*) New Researches on the Nature and Treatment of Local Asphyxia of the Extremities, Arch. gén. de méd. **1**:5 and 189, 1874.

2. Boardman, W. P.: Scleroderma, with Special Reference to Its Etiology and Treatment, Arch. Dermat. & Syph. **19**:901 (June) 1929.

the difficult therapeutic problem and the severity of the clinical course in this condition. It is not my purpose to review the vast literature on this subject or to discuss the many unproved theories concerning the etiology of sclerodactylia, since several excellent clinical reviews have been made.[3]

REVIEW OF THE LITERATURE

The fibrotic changes are not necessarily limited to the fingers but may be generalized. If the face is involved, it may be impossible for the patient to open his mouth completely or wrinkle his forehead. Osler [3e] described the characteristic condition of these patients as "encased in an evershrinking, slowly contracting skin of steel."

In the rare pathologic reports made in cases of generalized scleroderma, increased fibrosis of the internal organs, such as the lungs, kidneys and bladder, has been described. Histologic examination of the skin shows hypertrophy of the collagen and the stratum granulosum. The malpighian layer is atrophied, while the corium consists of masses of white and elastic fibers.[4]

Adson, O'Leary and Brown [5] recommended sympathectomy for the relief of sclerodactylia. The results of and indications for this operation will be considered in this paper. Kerr [6] found that repeated exposure of the fingers to cold water may reeducate the vessels so that they do not go into spasm so readily. He found that this procedure is without value if sclerodactylia is present.[7]

---

3. (*a*) O'Leary, P. A., and Nomland, R.: A Clinical Study of One Hundred and Three Cases of Scleroderma, Am. J. M. Sc. **180**:95, 1930. (*b*) Boardman.[2] (*c*) Lewin, G., and Heller, J.: Die Sclerodermie eine monographische Studie unter Zugrundelegung von 459 aus der Literatur gesammelter und eigener Fälle, Charité-Ann. **19**:763, 1894. (*d*) Longcope, W. T.: Hypoglycemia in Scleroderma, J. A. M. A. **90**:1 (Jan. 7) 1928. (*e*) Osler, William: On Diffuse Scleroderma, with Special Reference to Diagnosis, and to the Use of Thyroid-Gland Extract, J. Cutan. & Genito-Urin. Dis. **16**:49 and 127, 1898. (*f*) Durham, R. H.: Scleroderma and Calcinosis, Arch. Int. Med. **42**:467 (Oct.) 1928.

4. (a) Matsui, S.: Ueber die Pathologie und Pathogenese von Scleroderma universalis, Mitt. a. d. med. Fakult. d. k. Univ. zu Tokyo **31**:55, 1924; Presse méd. **2**:142, 1924. (*b*) Rake, Geoffrey: Pathology and Pathogenesis of Scleroderma, Bull. Johns Hopkins Hosp. **48**:212, 1931. (*c*) Gordon, H.: Diffuse Scleroderma, with Case Report and Autopsy Findings, Ann. Int. Med. **2**:1309, 1929.

5. Adson, A. W.; O'Leary, P. A., and Brown, G. E.: Surgical Treatment of Vasospastic Types of Scleroderma by Resection of Sympathetic Ganglia and Trunks, Ann. Int. Med. **4**:555, 1930.

6. Kerr, W. J.: Raynaud's Disease: Recent Experimental Studies, California & West. Med. **34**:91, 1931.

7. Kerr, W. J.: Personal communication to the author.

In addition to a more severe clinical course and a more difficult therapeutic problem, Lewis and Kerr [8] and Lewis and Landis,[9] in an exhaustive and admirable study of Raynaud's disease, found pathologic vascular reactions in the severe forms associated with sclerodactylia (cases 1, 2 and 3 of the series of Lewis and Kerr) which were not present in the mild type (cases 6, 7, 8 and 9 of the same series).[10]

Two main theories have been advanced as an explanation of the difference in behavior in the cases in which scleroderma was present and the cases in which it was not. In the report of Lewis and Kerr it was suggested that in the severe forms with sclerodactylia there is incomplete relaxation of the arteries between the attacks of spasm, while in mild types there is complete relaxation. Later Lewis suggested that severe forms present structural changes in the arterial walls, resulting in premature closure. A few reports have been made on structural changes in the digital arteries in Raynaud's disease [11] and in scleroderma.[12] These changes vary in frequency and intensity and may be absent in either condition. It cannot be denied, however, that when present arterial changes are an important factor in the circulatory defects of the severe forms of the disease. It is also probable that some of the pathologic vascular responses to be described are due in part to organic arterial changes.

---

8. Lewis, T., and Kerr, W. J.: Experiments Relating to the Peripheral Mechanism Involved in Spasmodic Arrest of the Circulation in the Fingers, a Variety of Raynaud's Disease, Heart **15**:7, 1929.

9. Lewis, T., and Landis, E. M.: Further Observations upon a Variety of Raynaud's Disease, with Special Reference to Arteriolar Defects and to Scleroderma, Heart **15**:329, 1931.

10. Lewis and Landis [9] stated that such severe scleroderma developed two years after the first observation in case 1, reported in the earlier series,[8] that the patient could not throw her head back because of the extreme tightness of the skin. The fingers were smaller and distinctly tenser than normal. In case 2 in the same series flexion of the fingers was possible only in the fourth and fifth fingers because of the tightness of the skin, while in case 3 the condition had grown worse, so that complete flexion of the fingers was impossible, owing to changes in the skin.

11. (*a*) Dinkler, M.: Zur Lehre von der Scleroderma, Deutsches Arch. f. klin. Med. **48**:514, 1891. (*b*) Spurling, R. G.; Jelsma, F., and Rogers, J. R.: Observations in Raynaud's Disease, Surg., Gynec. & Obst. **54**:584, 1932. (*c*) Grenet, H., and Isaac-Georges, P.: Etude histologique des artérioles cutanées dans trois cas de syndrome de Raynaud, Bull. et mém. Soc. méd. d. hôp. de Paris **50**:151 (Jan. 29) 1926.

12. (*a*) Matsui.[4a] (*b*) Lewis and Landis.[9] (*c*) Dinkler.[11a] (*d*) Whitehouse, H. H.: Some Observations on the Results of the Wassermann Test in Scleroderma, J. Cutan. Dis. **27**:535, 1909. (*e*) Durham, R. H.: A Case of Scleroderma with Extensive Subcutaneous, Periarticular and Vascular Calcification, Ann. Clin. Med. **5**:679, 1926.

PROBLEM OF INVESTIGATION

After a study of several patients with severe Raynaud's disease, one is impressed with the tight, inelastic condition of the skin found in some cases. The hypothesis seems reasonable that the tight skin of the fingers may have a constricting effect on the blood vessels and may thereby be responsible in part for the profound ischemia present in these cases. This theory has been suggested in the past [13] but has never been critically analyzed.

Two factors tend to make the tightness of the skin more deleterious to the circulation of the fingers than to the circulation of other areas. Owing to the circular shape of the fingers, the pressure of the skin is transmitted from all sides directly to the blood vessels. If an equal pressure is transmitted to only one side of the wall of a vessel, as may occur in parts of the body where the surface is relatively flat, only slight compression results. Moreover, the arterial blood pressure of the fingers at the level of the heart is considerably lower than the pressure in the larger and more central arteries, such as the brachial artery. Thus, it requires less external pressure to cause compression of the arteries of the fingers than compression of the larger arteries.

The theory that the tight condition of the skin and subcutaneous tissue has a constricting effect on the blood supply of the fingers in sclerodactylia has been investigated by the following observations made in cases of sclerodactylia and by artificial production of the mechanical effects of sclerodactylia on normal digits.

Investigation was made in five cases of sclerodactylia. On the basis of Lewis and Pickering's [14] classification of maladies grouped under the term Raynaud's disease, intermittent spasm of the digital arteries, with local nutritional changes, may be regarded as present in three instances. In these cases changes in the skin of the fingers occurred only after several years of typical intermittent spasm of the digital arteries, as indicated by the histories. The skin elsewhere was normal. In two cases mild generalized scleroderma was present. In all the cases the sclerodactylia was in a sufficiently advanced stage to cause marked limitation of motion of the fingers, and atrophy of the bone could be seen on roentgen examination. Unilateral sympathectomy was performed in three cases (table 1).

---

13. Mayo, W. J., and Adson, A. W.: Raynaud's Disease, Thrombo-Angiitis Obliterans and Scleroderma, Ann. Surg. **96**:771, 1932.

14. Lewis, T., and Pickering, G. W.: Observations upon Maladies in Which the Blood Supply to Digits Ceases Intermittently or Permanently, and upon Bilateral Gangrene of Digits: Observations Relevant to So-Called "Raynaud's Disease," Clin. Sc. **1**:327, 1934.

OBSERVATIONS IN CASES OF SCLERODACTYLIA

The following observations show that the circulatory deficiency in sclerodactylia is maximal in cases in which the mechanical factor due to the tightness of the skin and subcutaneous tissue is greatest:

1. The appearance of the fingers strongly suggests that the skin is hard and inelastic. It cannot be picked up or wrinkled. It is paler than the normal skin, and Brown and O'Leary [15] observed diminution in the number of capillaries in this condition. It is almost impossible to stretch

TABLE 1.—*Clinical Data in Five Cases of Sclerodactylia*

Case, Sex, Age	Duration of Malady, Years	Fingers	Generalized Sclero-derma	Necrosis	Sympa-thectomy	Blood Pressure, Mm.	Roentgeno-grapnic Observations
1 F 52 yr.	8	Moderately severe sclero-dactylia; marked limi-tation of motion; no tapering; nails normal	None	Repeatedly observed	4 years before; Horner's syndrome	150/ 80	Absorption of tips of several terminal phalanges
2 F 27 yr.	8	Marked limi-tation of motion; mod-erate tapering; deformity of nails	Moderate	Repeatedly observed	5 years before; Horner's syndrome	120/ 70	Absorption of tips of 2 terminal phalanges
3 F 50 yr.	25	Marked sclerodac-tylia; almost complete limi-tation of motion; marked loss of substance of fingers	None	Observed in all fingers	Right side; Horner's syndrome	140/ 70	Complete absorption of terminal phalanges of 3 fingers
4 F 45 yr.	5	Marked sclerodac-tylia; tapering; deformity of nails	None	Repeated ulcerations in winter	None	180/120	Slight ab-sorption of bone of tips of several terminal phalanges
5 M 51 yr.	7	Marked sclero-dactylia; marked loss of substance	Moderate	Repeated ulcerations	None	140/ 70	Complete absorption of bone of several terminal phalanges

the skin of a normal finger to the same degree as one can that of a finger with sclerodactylia, but if the volar surface is pinched the skin on the dorsum becomes tight, pale and smooth and presents an appearance not unlike that of sclerodactylia.

Occasionally the sclerodermatous changes do not uniformly involve all the fingers. Determinations of the cutaneous temperature verify this observation. The finger with the least disturbance of the skin is warmer than its more unfortunate fellows. A further observation is significant.

15. Brown, G. E., and O'Leary, P. A.: Skin Capillaries in Scleroderma, Arch. Int. Med. **36**:73 (July) 1925.

It has been adequately shown by Lewis and Kerr that one of the most characteristic features of sclerodactylia is complete, or almost complete, inability of the fingers to maintain normal cutaneous temperature. The fingers assume and slavishly follow room temperature. It may be seen from the graph in figure 1 that the temperature of the finger with severe changes in the skin follows the room temperature as the room is cooled but that the less affected finger cools only gradually—a reaction not unlike that of the normal skin.[16]

2. In case 3 in this series it was repeatedly noted that the tips of the fingers became dead white when the fingers were extended. On flexion the color of the skin immediately changed to that of the rest

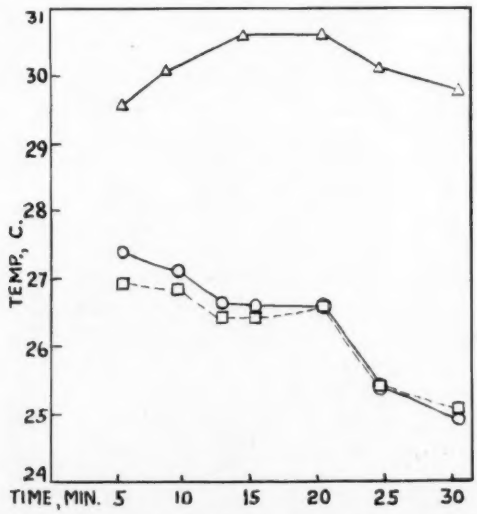

Fig. 1 (case 1).—Effect of room temperature on the temperature of the skin of a digit (third on the left hand) with severe sclerodactylia and on that of a digit (first on the left hand) with slight sclerodactylia. In this chart and in the accompanying charts, except in figure 11, the curve for room temperature is indicated by a line and squares. The curve for the digit with severe sclerodactylia is indicated by a line and circles, and the curve for the digit with mild sclerodactylia, by a line and triangles. At the twentieth minute a window was opened to cool the room.

of the fingers. If while the finger was extended, gentle upward pressure was exerted on the middle phalanx, thereby relaxing the skin at the tip, the color again changed. With the use of Lewis' color scale[17] it was

16. Freeman, H., and Linder, F. E.: Some Factors Determining the Variability of Skin Temperature, Arch. Int. Med. **54**:981 (Dec.) 1934.

17. Lewis, T.: Standard Colours for Use in the Study of Vascular Reactions of the Human Skin, Heart **15**:1, 1929.

estimated that the intensity of the color of the skin of the finger-tip changed from tint *j* when the skin was taut to tint *e* or *d* when it was relaxed. The cutaneous temperature of this patient's finger-tips was repeatedly determined. When the fingers were extended, the temperature of the tips was always slightly below room temperature.[18] When the fingers were flexed, the temperature immediately rose slightly above room temperature (fig. 2). The marked increase in ischemia on extension of the fingers in this case was obviously due to the tight, inflexible condition of the skin.

3. Atrophy of the terminal phalanx has been described repeatedly.[19] The atrophy begins at the very tip and proceeds proximally until the entire terminal phalanx is absorbed (fig. 3). The atrophy never starts at the base of the terminal phalanx, as might occur if the disturbance were metabolic, nor is the process diffuse, as in the well known atrophy of disuse. The absorption of the bone corresponds to the areas of

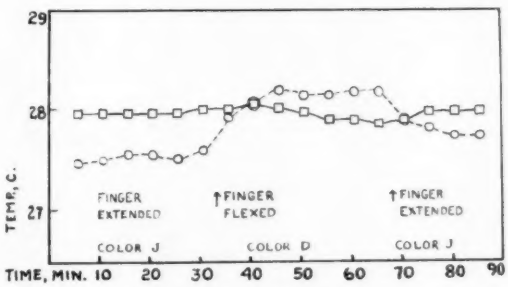

Fig. 2 (case 3).—Effect of flexion and extension of the fingers on the temperature and color of the skin. After thirty-five minutes of extension the fingers were flexed. At the sixty-fifth minute they were again extended. In this chart the curve for the digit (fourth on the left hand) is indicated by a dotted line and circles.

greatest pressure of the skin, and the best explanation is that the process is similar to the atrophy which occurs in other bones subjected to persistent pressure. Christian [20] has expressed a somewhat similar opinion.

4. Vasodilatation as a result of sympathectomy does not improve the circulatory deficiency in sclerodactylia. As already pointed out, a characteristic feature of the very severe form is the close approximation of the temperature of the affected fingers to room temperature. In the

18. Room temperature was taken with a thermocouple from 1 to 3 cm. from the skin.

19. (*a*) Edeiken, L.: Scleroderma with Sclerodactylia, Am. J. Roentgenol. **22**:42, 1929. (*b*) Osler.[3e] (*c*) Fox, G. H.: Two Cases of Raynaud's Disease with Ocular Symptoms, J. Cutan. Dis. **25**:337, 1907.

20. Christian, H., in discussion on Longcope.[3d]

moderately severe type the temperature of the skin may rise slightly above that of the room. It has been adequately shown that sympathectomy raises the temperature of the skin of normal subjects and of patients with mild Raynaud's disease by producing arterial dilatation. In three patients with an advanced stage of sclerodactylia no increase in the temperature of the skin could be observed, and the fingers both on the side of sympathectomy and on the side on which no operation was performed always assumed room temperature. Though the sympathetic tone of the arteries is lost, the vessels cannot open, owing to the tightness of the skin. The patients noticed no clinical improvement, and the attacks of gangrene were equally intense on the two sides. Needless to say, the patients refused to undergo operation on the opposite side.[21]

Fig. 3 (case 3).—Roentgenogram of the hands in a case of typical sclerodactylia. The atrophy begins at the tips of the terminal phalanges (third and fifth fingers of the left hand) and progresses proximally until the entire terminal phalanx is absorbed (second finger of the left and right hand).

In view of these considerations, sympathectomy appears irrational in the treatment of this disease. Though it is assumed that there is no organic occlusion, dilatation of the vessels to any great degree is a physical impossibility because of the tight skin. More evidence will be offered on this point.

OBSERVATIONS ON NORMAL DIGITS

Method of Investigation.—The mechanical effects of sclerodactylia may be produced by placing a tight rubber finger from a small surgical glove on the finger to be studied. (Size 6½ was generally used for a finger that normally required

21. The operation was performed four years prior to the time of writing (1930) in the three cases.

size 7½ or 8.) In other instances the finger was bound with small strips of zinc oxide adhesive tape. This method of producing compression is probably better, since the adhesive tape is inelastic and does not expand with each systole. It is difficult to evaluate the amount of compression which such constriction causes. On the basis of evidence which will be given later, the pressure produced with the second method is equivalent to about 70 mm. of mercury, which is considerably above the diastolic pressure in the fingers, but below the systolic pressure. An effort was made to keep the pressure the same in all the experiments. The glove caused a uniform compression of the finger, which was estimated to be of about the same intensity as that found in the severe forms of sclerodactylia. A small opening was made in the glove over the dorsal surface of the terminal phalanx just proximal to the nail for determinations of the temperature of the skin. If it was desired to determine the color of the skin, the opening was made on the ventral surface. The finger may be bound for hours without causing more than a feeling of constriction. As a control, a loose glove finger was placed on the corresponding digit of the other hand.

Temperature of the Skin.—As has already been pointed out, Lewis and Kerr found that a characteristic feature of the severe form of Raynaud's disease associated with sclerodactylia is the inability to maintain the normal temperature of the skin, an observation I have confirmed. In the mild forms, with no cutaneous changes, the temperature of the skin is normal unless the critical cold point which produces spasm is reached.

After a period of preliminary observation, the constriction already described was placed on the second finger, while a loose glove was placed as a control on the corresponding finger of the other hand. The temperature of the skin of the finger with the artificial sclerodactylia gradually decreased to room temperature, while the temperature of the finger used as a control remained several degrees above room temperature. If the room temperature was changed by opening or closing a window, the temperature of the skin of the bound finger closely followed the room temperature. If the bound finger and the finger used as a control were placed in warm water at from 40 to 45 C. for from five to ten minutes, the finger used as a control quickly assumed its former temperature on removal, while the temperature of the bound finger slowly fell to that of the room. If both fingers were then placed in water at 20 C. for five minutes, the temperature of the bound finger merely rose again to room temperature on removal, while the temperature of the control finger quickly attained its former value (fig. 4). If the tight glove was removed, the temperature of the skin rapidly rose above the temperature of the control finger. This is due to the well known phenomenon of reactive hyperemia, and the test demonstrates that complete arterial occlusion is not necessary to produce the phenomenon.

Effect of Overcooling.—If after preliminary cooling to approximately from 23 to 25 C. (73.4 to 77 F.) the finger is placed in ice-

water for from five to ten minutes, the blood vessels dilate considerably, and the finger subsequently becomes hotter than the control finger.[22] This reaction was found to be normal in cases of mild Raynaud's disease; in cases in which the disease is associated with sclerodactylia, however, Lewis and Kerr found that the temperature of the skin does not overshoot but merely rises to room temperature, an observation which we have confirmed.[23]

This observation may be repeated with the experimental method. The finger with the loose rubber glove, used as a control, reacts normally, while we have repeatedly observed that the temperature of the bound finger, after exposure to ice water, does not overshoot but shows a response identical to that occurring in the cases of Raynaud's disease with sclerodactylia (fig. 5).

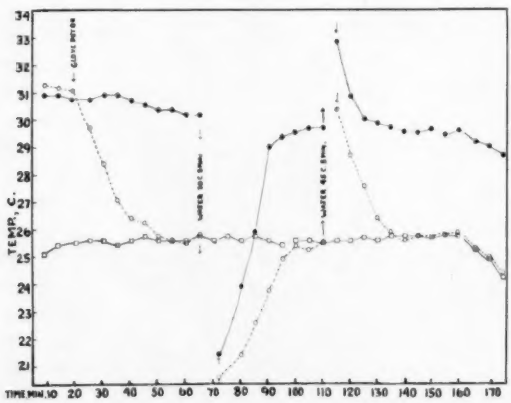

Fig. 4.—Effect of constriction of a normal finger on the temperature of the skin. At the twentieth minute the first finger of the left hand was bound. At the sixtieth minute both the bound finger and the finger used as a control were placed in water at 20 C. for five minutes. At the one hundred and tenth minute the fingers were placed in water at 45 C. for five minutes. At the one hundred and sixtieth minute the room was purposely cooled by opening a window. In this chart and in the charts in figures 5, 6 and 8 the curve for the finger in which artificial scleroderma was produced (first digit of the left hand in this experiment) is indicated by a dotted line and circles, and the curve for the finger used as a control (first digit of the right hand in this experiment), by a solid line and solid circles.

22. Lewis, T.: Observations upon the Reactions of the Vessels of the Human Skin to Cold, Heart **15**:177, 1930; Supplementary Notes upon the Reactions of the Vessels of the Human Skin to Cold, ibid. **15**:351, 1931; The Blood Vessels of the Human Skin and Their Response, London, Shaw & Sons, 1927.

23. Clifford Wilson and I have found that this reaction may be absent in some patients with peripheral vascular disease.

Volume of the Digital Pulse.—The volume of the digital pulse at different temperatures may be determined by means of a small finger plethysmograph. The oscillations are transmitted to a Frank capsule, magnified by an optical system and recorded on a moving photographic film. With this method changes in volume of 0.001 cc. may be determined. Tracings are taken at 20, 25, 30, 35, 40 and 45 C., respectively, after the finger has been exposed to each temperature for ten minutes. At the higher temperatures the magnitude of the oscillations is normally greatly increased because of arterial dilatation and increase in blood flow. Lewis and Kerr found that in cases of uncomplicated Raynaud's disease the curve is normal but that in cases in which the disease is associated with sclerodactylia the oscillations are greatly reduced at the higher temperatures.

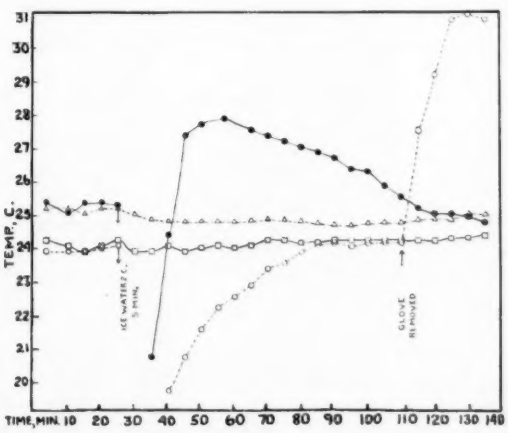

Fig. 5.—Effect of overcooling on the temperature of the skin. At the twenty-fifth minute both the bound finger (second digit of the left hand) and the finger used as a control (second digit of the right hand) were placed in ice-water for five minutes. On the one hundred and tenth minute the constriction was removed. The curve for a finger with mild sclerodactylia (fourth finger on the right hand) is indicated by a line and triangles.

This experiment was repeated many times with a finger in which artificial sclerodactylia was produced. The resulting curve is similar in all respects to the curves obtained by Lewis (fig. 6).

If the pressure on the finger is slight, the magnitude of the oscillations is greatly increased. This is probably due to better mechanical transmission of the pulse beat and is analogous to the increase in the magnitude of the pulsations obtained by a Pachon oscillometer when the pressure is considerably below the systolic.

The effect of pressure on the oscillations in the pulse volume was studied in the following manner:

The finger was placed in a glass tube closed at one end and connected by a side arm with a mercury manometer and an air-pump, so that any desired pressure could be obtained. Circular rubber tubing from a glove finger lightly grasped the

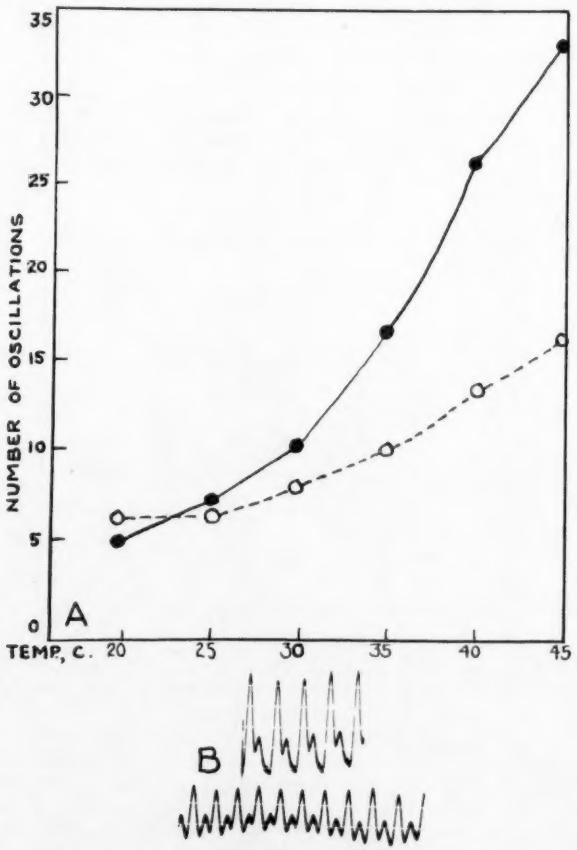

Fig. 6.—(*A*) Graph showing the effect of temperature on the plethysmographic oscillations of the pulse of a constricted finger and on those of the same finger with no constriction. The increment is 0.001 cc. (*B*) Tracings taken at 40 C. of the plethysmographic oscillations of the pulse of a normal finger (the upper tracing) and of the same digit while constricted (lower tracing).

proximal end of the finger and the glass tube so that when the pressure was raised the opening was sealed and a uniform pressure was exerted on the entire finger. The tube was filled with water at a known temperature. The level of

the water was read in the narrow side arm and the pulsations were observed. The pressure in the tube could be changed at will, and the effect of various pressures on the pulsations observed (fig. 7).

At a pressure of from 20 to 50 mm. of mercury the oscillations were greatly increased over the normal, the greatest being obtained at from 30 to 50 mm. of mercury. At a pressure above 60 mm. of mercury the oscillations became smaller than normal, until they completely disappeared at from 90 to 100 mm. of mercury, the systolic pressure of the fingers at the level of the heart. From this observation it is obvious that the pressure exerted on the finger in these experiments is from 60 to 90 mm. of mercury. It is not lower, for the oscillations were smaller than normal. It is below 90 mm. of mercury, or systolic pressure, for pulsations were present.

Sympathetic Vasodilatation.—It has been shown by Lewis [24] that if the body is heated after preliminary cooling sympathetic vasodilatation

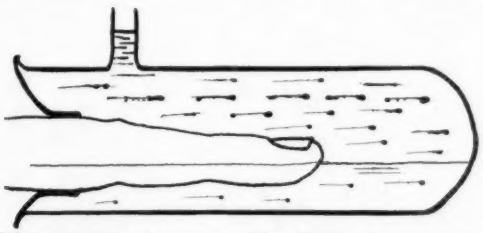

Fig. 7.—Diagram of the glass tube. The side arm is connected with a mercury manometer and a hand air-pump.

of the arterioles of the extremities takes place and that this reaction may be used as a test for occlusive arterial disease. Landis and Gibbon [25] modified this procedure by placing one or two extremities in hot water and measuring the temperature of the skin of the limb to be tested. If the cutaneous temperature of this limb does not rise appreciably, it is assumed that an organic arterial lesion is present. In cases of sclerodactylia we have found that no rise in temperature takes place. In the following experiment it was shown that tight skin, such as occurs in sclerodactylia, may produce the same type of reaction as organic arterial occlusion:

A tight binding was placed on a finger and a loose binding on a finger to be used as a control, after preliminary cooling. Both feet

24. (*a*) Lewis, T.: Experiments Relating to Peripheral Mechanism Involved in Spasmodic Arrest of Circulation in the Fingers: A Variety of Raynaud's Disease, Heart **15**:7, 1929. (*b*) Lewis, T., and Pickering, G. W.: Vasodilatation of the Limbs in Response to Warming the Body, Heart **16**:33, 1933.

25. Landis, E. M., and Gibbon, J. H., Jr.: Simple Method of Producing Vasodilatation in Lower Extremities, with Reference to Its Usefulness in Studies of Peripheral Vascular Disease, Arch. Int. Med. **52**:785 (Nov.) 1933.

were then placed in water at from 43 to 45 C. The control finger reacted normally and soon reached a temperature of 32 C. (89.6 F.). The temperature of the bound finger, which had previously been that of the room, rose only 1.5 C. (2.7 F.). Another characteristic may be noted. While the control finger began to react from ten to fifteen minutes after the feet were placed in hot water, the bound finger did not react until ten minutes later, an observation which Landis made in cases of organic occlusion (fig. 8). If the constriction was slightly more intense, no increase in the temperature of the finger took place.

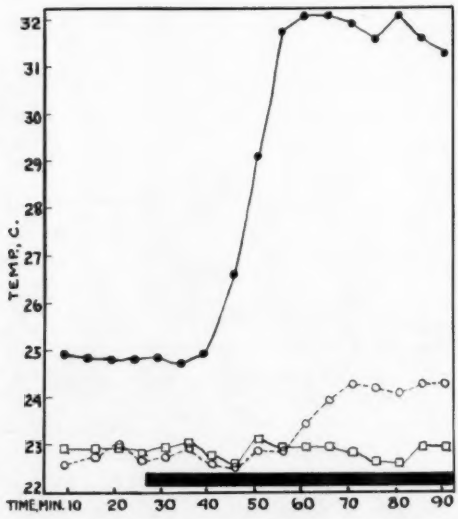

Fig. 8.—Effect of the Landis test on the temperature of the skin of the finger used as a control (second on the right hand) and of the bound finger (second on the left hand). At the twenty-sixth minute, as indicated by the solid rectangle, the left foot was placed in warm water at a temperature of from 43 to 45 C.

These observations support my explanation of the lack of therapeutic response to sympathectomy in cases of sclerodactylia, and they further show the irrationality of the procedure in the treatment of this condition.

Effect of Histamine.—We have observed that if from 0.1 to 0.2 cc. of a mixture of a 1:1,000 dilution of histamine hydrochloride and a small amount of procaine hydrochloride is slowly injected into the terminal phalanx of a finger or toe after preliminary cooling, the temperature of the skin around the site of injection rapidly rises to the maximum. If an organic arterial lesion is present, the increase is greatly

reduced or is absent. We have used this test in several cases of peripheral vascular disease in order to determine the degree of spasm. In all cases in which tests have so far been made, we have found complete correlation between the results of this test and those of the Landis test (fig. 9). The main advantage of this test is its simplicity and the rapidity with which it can be performed.

If this test is performed on patients with an advanced stage of sclerodactylia, no rise in temperature takes place (table 2).[26] In cases of uncomplicated Raynaud's disease there is a normal rise in temperature. If a normal finger is bound in the manner already described, there is little or no increase in temperature, while the normal reaction takes place in the finger used as a control.

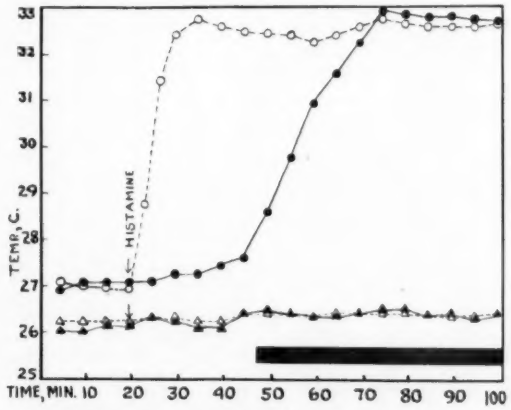

Fig. 9.—Effect of the injection of 0.2 cc. of histamine on the temperature of the skin of the extremities of a patient with thrombo-angiitis of the lower extremities. The injections were made in the first toe of the right foot and the fourth finger of the right hand. The lack of response of the temperature of the toes and the rapid increase in the temperature of the fingers are shown. At the forty-sixth minute, as indicated by the black rectangle, the left arm was placed in warm water at a temperature of from 43 to 45 C. as a control test, with identical results. The room temperature varied from 23 to 25 C. In this chart the curve for the first toe of the right foot is indicated by a line and hollow triangles; the curve for the second toe of the same foot, by a line and solid triangles; the curve for the third finger of the right hand, by a line and solid circles, and the curve for the fourth finger of the right hand, by a line and hollow circles.

26. We have recently observed an increase in temperature of 1.5 C. (2.7 F.) after the injection of histamine in a patient with sclerodactylia, who was not included in this series. There had been no rise in temperature following the heat test performed by the Landis technic. After an injection of histamine into a finger, it was impossible to induce an attack of arterial spasm in that finger by exposure to cold water.

Effect on Blood Flow of Alteration in Atmospheric Pressure.—There has been a recent revival of altering the atmospheric pressure as a therapeutic procedure to increase the blood flow to the extremities [27] in disease of the peripheral arteries. It has been shown that the blood flow, as measured by the temperature of the skin, may be greatly increased by this procedure and that spectacular benefit often results. In Raynaud's disease a somewhat similar method has been tried, apparently with great success,[28] but, unfortunately, not under controlled experimental conditions. We have made the following observations in regard to this therapeutic procedure:

A binding was placed on the finger sufficiently tight to cause enough compression to eliminate any rise in the temperature of that finger during the Landis

TABLE 2.—*Temperatures of the Skin of the Fourth Fingers of the Left and Right Hands in Case 4 During the Landis Test and After Injection of Histamine* *

Time	Room Temperature, C.	Temperature of Left Finger, C.	Temperature of Right Finger, C.
10:15	29.2	30.7	28.7
10:20	27.5	30.4	28.6
10:25	24.5	26.8	26.3
10:30	22.7	24.4	24.2
10:35	20.2	20.5	20.3
10:40	20.1	20.3	20.2
10:50	20.4	20.4	20.2
10:55	20.5	20.5	20.6
11:00	20.7	20.9	20.9
11:05	21.4	20.7	20.7
11:10†			
11:15	20.0	19.5	19.5
11:20	19.3	19.1	18.8
11:30	19.2	18.7	18.7
11:40	19.3	18.7	18.5
11:50	20.2	19.7	19.4
12:00	20.5	19.7	19.5
12:10	20.6	19.6	19.7
12:20	20.9	19.9	19.8‡
12:30	21.2	20.1	20.0
12:40	21.3	20.1	20.0

* No dilatation of the arteries followed either test.
† Both feet in water, 45 C.
‡ Injection of 0.2 cc. of a 1:1,000 dilution of histamine hydrochloride and procaine hydrochloride into the right finger.

test or after the injection of histamine. Thus, sympathetic vasodilator impulses could not increase the blood flow. The digit was then placed in a small glass plethysmograph, which was connected to a vacuum pump. A pressure of —100 mm. of mercury was maintained for fifteen seconds, alternating with a pressure of 0 or of +10 mm., held for a shorter period.

27. (*a*) Landis, E. M., and Gibbon, J. H.: Effects of Alternate Suction and Pressure in Circulation in the Lower Extremities, Proc. Soc. Exper. Biol. & Med. **30**:593, 1933. (*b*) Reid, M. R., and Herrmann, L. G.: Treatment of Obliterative Vascular Disease by Means of Intermittent Negative Pressure Environment, J. Med. **14**:200, 1933. (*c*) Herrmann, L. G., and Reid, M. R.: The Pavaex Treatment of Obliterative Arterial Disease of the Extremities, ibid. **14**:524, 1933. (*d*) Herrmann, L. G.: Syphilitic Peripheral Vascular Diseases, Am. J. Syph. & Neurol. **17**:305, 1933.

28. Braeucker, W.: Die Behandlung der Raynaudschen Krankheit, Arch. f. klin. Chir. **167**:807, 1931.

It was found that a slight rise in the temperature of the skin of about 1.5 C. (2.7 F.) often took place and that improvement in the color of the skin occurred (fig. 10). This increase in circulation, although slight, is of significance, since sympathetic vasodilator impulses induced by the Landis test were insufficient to open the compressed arterioles but the suction apparently partially relaxed the artificial compression, allowing more blood to flow into the finger.

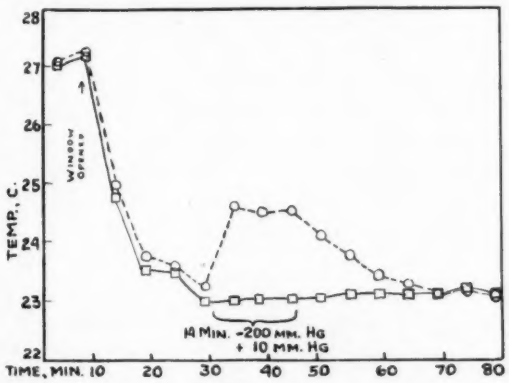

Fig. 10.—Effect of alteration of the atmospheric pressure on the temperature of the skin of a constricted finger. No rise in temperature took place during the Landis test or after injection of histamine which had been made prior to the constriction. In this chart the curve for the constricted finger is indicated by a line and hollow circles.

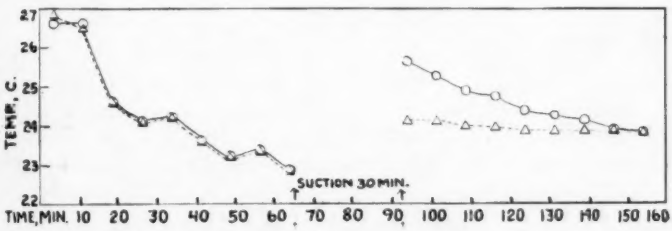

Fig. 11.—Effect of altering the atmospheric pressure in case 3. No increase in the temperature of the skin followed sympathectomy, which had previously been performed. In this chart the curve for room temperature is indicated by a dotted line and triangles, and the curve for the constricted finger (fourth on the left hand) by a solid line and circles.

We have had the opportunity of studying this procedure in a patient with sclerodactylia after complete unilateral sympathectomy, a procedure which, as already shown, had not the slightest effect on the

temperature of the skin (case 3). That the sympathetic nerves were cut was proved by the inability of the patient to perspire on the side of operation and by the presence of the Horner syndrome. Suction caused a definite improvement in the color of the skin, especially in the intensity, and there was a slight but definite rise in the temperature of the skin above that of the room (fig. 11). This is the only procedure we were able to discover which increased the blood supply of the fingers of this patient. Tingling of the fingers frequently occurs during the treatment. Lewis and his associates [29] showed that this is due to recovery of the nerves from loss of blood supply.

When an attack of arterial spasm was produced in the fingers by prolonged exposure to water at 15 C., we were unable to relieve the spasm by this procedure in two instances. In one patient the area of cyanosis increased during the suction. On the basis of these observations, it is not likely that this procedure has any therapeutic benefit in cases of uncomplicated Raynaud's disease.

COMMENT

From the review of the literature it is apparent that Raynaud's syndrome may be divided into two fairly distinct types, which differ clinically, therapeutically and experimentally. In the form associated with sclerodactylia the clinical picture is more severe; the therapeutic problem is more difficult, and the experimental vascular reactions differ from those in the uncomplicated form. In spite of these differences, there is a fundamental similarity in that there are attacks of cyanosis and blanching on exposure to cold in both types.

We believe that we have demonstrated that the mechanical effects of tight skin are sufficient to explain the severe clinical course, the difficult therapeutic problem and the pathologic vascular response found in sclerodactylia. In addition, morphologic studies have shown that arterial lesions, which undoubtedly aggravate the condition, may be present. The relative importance of each factor cannot be ascertained at present. If cases of Raynaud's disease are found in which normal skin but abnormal vascular responses occur, one may be sure that arterial changes are present. If the vascular reactions are normal, no marked arterial lesions or changes in the skin are present.

It seems reasonable to assume that the ischemia produced by a tight skin is more severe than that induced by organic arterial lesions, since, in addition to a decrease in the blood flow, there is compression of the capillaries, which diminishes the nutrition of the tissues.

29. Lewis, T.; Pickering, G. W., and Rothschild, P.: Centripetal Paralysis Arising Out of Arrested Blood Flow to the Limb, Including Note on a Form of Tingling, Heart **16**:1, 1933.

In all the roentgenograms taken in the cases in our series, the interphalangeal joints appeared normal. It is therefore probable that the marked limitation of motion of the fingers is due to the fibrosis which splints the finger rather than to arthropathy.

In view of these observations, the rational therapeutic approach to Raynaud's disease in association with sclerodactylia may be considered. As indicated early in this paper, sympathectomy offers no hope for relief. Reeducation by exposure to cold and the use of vasodilator drugs, procedures which are recommended in cases of Raynaud's disease in which no complications occur, are also ineffective. Until an agent is found which reduces fibrous tissue and remedies organic changes in the arteries, treatment at best is unsatisfactory and can be only symptomatic. It occurred to us that if the skin could be split longitudinally on the lateral and medial surfaces of the fingers, the edges of the tight skin might retract and thereby allow the vessels to expand. We hoped to fill the defect by means of a skin graft. In one patient (case 5),[30] on whom Dr. J. Homer Woolsey operated in this manner, no retraction of the skin took place. The scar tissue in this case at least extended all the way to the bone, and improvement did not occur. If conditions can be found in which the fibrosis involves only the skin, this procedure may be beneficial.

The most rational procedure seems to be the alternating use of suction and compression, as recommended by Herrmann and Landis. We have shown not only experimentally but clinically that this procedure may increase the blood flow to the fingers when other procedures, including sympathetic vasodilatation, fail. The mechanism of improvement in these cases is probably the stretching of the skin, which permits better blood flow. We are unprepared to state whether this procedure will prove beneficial in all cases, nor are we sure how great the degree of benefit will be.

CONCLUSIONS

1. Raynaud's syndrome in association with sclerodactylia has a more severe clinical course and presents a more difficult therapeutic problem than uncomplicated Raynaud's disease, and the experimental vascular reactions differ in the two conditions.

2. Important causal factors in sclerodactylia are the tight, inelastic skin and subcutaneous tissue of the fingers, which constrict the blood vessels and diminish the blood flow.

3. In sclerodactylia the areas of greatest circulatory insufficiency coincide with the areas of greatest change in the skin. Determinations of the temperature of the skin verify this contention.

30. This patient was in the medical service of Dr. William J. Kerr of the University of California Hospital.

4. Evidence is presented which indicates that the atrophy of the terminal phalanx in sclerodactylia is probably due to pressure of the tight skin.

5. Whereas sympathectomy raises the temperature of the normal skin and the temperature of the skin of patients with uncomplicated Raynaud's syndrome, little or no rise in temperature takes place if severe sclerodactylia is present, and no clinical improvement follows. An important factor in this result is the tight skin which constricts the vessels and does not permit dilatation of the arteries after vasomotor tone is abolished.

6. It was demonstrated in one case that if the tight skin of the finger tip is relaxed, slight but definite improvement in circulation, as determined by the color and temperature of the skin, takes place.

7. If a binding of about the same degree of tightness as that present in sclerodactylia is placed on a normal finger, the abnormal vascular reactions found in sclerodactylia may be duplicated. It has been shown by this method that the temperature of the skin assumes and follows room temperature, the characteristic vasodilator phenomenon on exposure to cold is not shown and smaller plethysmographic oscillations occur at high temperatures.

8. Vasodilator impulses induced by the Landis heat test for arterial occlusion cause little or no increase in the temperature of the skin in sclerodactylia. Similarly, if a normal finger is bound, little or no rise in temperature takes place.

9. A simple test for arterial occlusion may be performed by the injection of histamine into the terminal phalanx of the finger or toe to be tested. If no organic occlusion is present, the temperature of the skin rises in a short time.

10. In cases of severe sclerodactylia no rise in temperature takes place after the injection of histamine. If the normal finger is bound, similar results are obtained.

11. The use of intermittent suction, recommended by Herrmann and Landis, may cause an increase in circulation in cases of sclerodactylia, as determined by the temperature and color of the skin, though sympathectomy has failed to produce improvement. It is suggested that the mechanism of improvement is the relaxation of the tight skin. This seems to be the only method available at present which may prove beneficial. This procedure is probably ineffective in the relief of attacks of uncomplicated Raynaud's disease.

Dr. George E. Wever, San Francisco, and Dr. Florence Haynes, Boston, gave help in various experiments. Dr. James C. White of the Massachusetts General Hospital gave permission for the study of three of his cases.

Progress in Internal Medicine

INFECTIOUS DISEASES

REVIEW OF THE CURRENT LITERATURE

HOBART A. REIMANN, M.D.
PHILADELPHIA

The labor of reviewing the literature on infectious diseases has been considerably lightened by the recent publication of a number of comprehensive surveys covering various aspects of the subject.[1] Notable among these are reviews concerning gonococcic infections, arthritis, bacteriophage, lymphogranuloma venereum (lymphogranuloma inguinale), influenza, undulant fever and Weil's disease. Advances in the knowledge of syphilis and microbic dissociation will be discussed in forthcoming papers.[2] The portions of the subjects dealt with in these papers will therefore not be discussed in the present review.

PNEUMONIA

According to various statistics, pneumonia occupies second or third place in tables of mortality rates and is responsible for about 100,000 deaths a year in the United States. Hence, any advances in its prevention or treatment are of great significance. The seriousness of the problem led to an intensive study over a four year period in Massachusetts, and recently campaigns against this disease have been inaugurated in the states of New York, Connecticut and Maine and in Detroit. Because of the favorable results obtained by physicians in general prac-

From the Department of Medicine, Jefferson Medical College.

1. Thomas, R. B., and Bayne-Jones, S.: Report of the Committee for Survey of Research on the Gonococcus and Gonococcus Infection, Am. J. Syph., Gonor. & Ven. Dis. (supp.) **20**:1-179 (Jan.) 1936. Hench, P. S.; Bauer, W.; Fletcher, A. A.; Ghrist, D.; Hall, F., and White, T. P.: Present Status of the Problem of "Rheumatism" and Arthritis, Ann. Int. Med. **9**:883-982 (Jan.) 1936. Krueger, A. P.: The Nature of Bacteriophage and Its Mode of Action, Physiol. Rev. **16**:129-172 (Jan.) 1936. Wassén, E.: Studies of Lymphogranuloma Inguinale from Etiological and Immunological Points of View, Acta path. et microbiol. Scandinav. (supp.) **23**:1-168, 1935. Klotz, O., and Holman, W. L.: Studies on Influenza, Am. J. M. Sc. **191**:426-446 (March) 1936. Carpenter, C. M., and Boak, R. A.: The Treatment of Human Brucellosis: A Review of Current Methods, Medicine **15**:103-127 (Feb.) 1936. Jeghers, H. J.; Houghton, J. D., and Foley, J. A.: Weil's Disease, Arch. Path. **20**:447-476 (Sept.) 1935.

2. Moore, J. E.: Syphilis: A Review of the Recent Literature, Arch. Int. Med., to be published. Hadley, P.: Physiol. Rev., to be published.

tice with the typing of pneumococci and specific serum therapy, Massachusetts has undertaken to supply antiserum for typing and therapeusis free of charge. The results of the study have been summarized in a handbook.[3]

The practice of regarding pneumonia from an etiologic point of view is constantly gaining ground. It is well established that the term pneumonia includes a group of acute infections of the lungs, each caused by specific organisms. The clinical characteristics of the forms of pneumonia due to pneumococci of types I, II, III and VIII which permit each to be regarded as an entity have already been described. During the year further reports have appeared. Smith [4] studied a small epidemic of staphylococcic pneumonia among infants in a Glasgow hospital. Bullowa [5] analyzed the results of his large experience with typing pneumococci and found that the organisms recovered from the sputum of patients with pneumonia were of the type responsible for the disease in over 93 per cent of cases, thus revealing the reliability of the methods in current use. The simple and rapid Neufeld capsule-swelling test, a test which can be used in office practice, was found to be reliable in 76 per cent of cases. Numerous investigators are depending more on puncture of the lung to obtain material for typing.[6] The difficulty of obtaining sputum from infants has been largely overcome by aspirating the swallowed sputum from the stomach by means of a small rubber tube.[7] Belk's [8] statistical study of the value of concentrated serum therapy shows a reduction of mortality due to type I infection from 25 per cent in cases in which the serum was not given to 15 per cent in the cases in which the serum was used; in type II infections the rate was reduced from 37 to 30 per cent. These figures are more impressive when the cases of bacteremia are analyzed separately. Large doses of antiserum are necessary in treating type II pneumonia.[8] In another study [3] serum treatment reduced the death rate in cases of type I infection from 25

3. Lord, F. T., and Heffron, R.: Lobar Pneumonia and Serum Therapy, New York, Commonwealth Fund, 1936.

4. Smith, C. M.: Staphylococcal Pneumonia Among Infants in a Maternity Hospital, Lancet **1**:1204-1207 (May 25) 1935.

5. Bullowa, J. G. M.: The Reliability of Sputum Typing and Its Relation to Serum Therapy, J. A. M. A. **105**:1512-1518 (Nov. 9) 1935.

6. Sappington, S. W., and Favorite, G. O.: Lung Puncture in Lobar Pneumonia, Am. J. M. Sc. **191**:225-234 (Feb.) 1936.

7. Witten, S. A., and Bullowa, J. G. M.: Gastric Aspiration in Children with Pneumonia to Obtain Material for Pneumococcus Typing, Am. J. Dis. Child. **50**: 1404-1408 (Dec.) 1935.

8. Belk, W. P.: The Specific Treatment of Lobar Pneumonia, J. A. M. A. **105**:868-871 (Sept. 14) 1935. Finland, M., and Dowling, H. F.: The Dose of Antibody Effective in the Treatment of Pneumococcus Type II Pneumonia, Am. J. M. Sc. **191**:658-673 (May) 1936.

to 11 per cent and in those of type II infection from 41 to 27 per cent. Thus far the greatest benefits have accrued from type I and type VII antiserum. Antiserum for infections of types IV, V, VI, VIII and XIV will soon be commercially available. Type VII infections accounted for about 6 per cent of the cases of pneumonia in Bullowa's [5] series, with an average mortality rate in cases of bacteremia in which serum was not administered of nearly 70 per cent, as compared with 25 per cent in cases in which serum was administered. Pneumonia due to the type VIII pneumococcus was usually less severe than that due to certain other types, especially type III, with which type VIII is closely related immunologically.[9] Goebel [10] has shown that the basis for this relationship may rest in the identity of the aldobionic acid nucleus common to the carbohydrate of these two types. Type VIII organisms invade the blood stream more frequently than those of type III, but fortunately with a much lower mortality. Type VIII pneumococci are prone to invade the meninges after subsidence of the pneumonia. The results of therapy with type VIII antiserum were striking. In 21 cases in which the serum was not used the mortality was 62 per cent; in the 12 cases in which it was used, 16 per cent. Cecil [11] recently analyzed 500 cases of type III pneumonia.

Pneumonia caused by Pneumococcus type XIV is especially common in young children, often being of the lobar form in infants, with prolonged illness.[12] In adults this type often causes severe illness, and the organism invades the blood, pleura, pericardium and meninges more frequently than many other types of pneumococci. Specific serum therapy appears to shorten the course of the illness.

An excellent small monograph describing the methods of typing and specific treatment of pneumonia has recently been published.[3]

Heterophile Antibodies.—Much unwarranted commercial publicity has been given to the use of antipneumococcus serum containing heterophile antibodies. On the basis of certain academic investigations this serum has been made available prematurely to the general practitioner without adequate clinical trial. While it is necessary and desirable to

9. Bullowa, J. G. M.: Pneumonias Due to Pneumococcus Type VIII, Am. J. M. Sc. **190**:65-83 (July) 1935.

10. Goebel, W. F.: Chemo-Immunological Studies on Soluble Specific Substance of Pneumococcus: II. Chemical Basis for the Immunological Relationship Between the Capsular Polysaccharides of Types III and VIII Pneumococcus, J. Biol. Chem. **110**:391-398 (July) 1935.

11. Cecil, R. L.; Plummer, N., and McCall, M.: Pneumococcus Type III Pneumonia: An Analysis of Five Hundred Cases, Am. J. M. Sc. **191**:305-319 (March) 1936.

12. Bullowa, J. G. M.: Pneumonia Due to Pneumococcus Type XIV (Cooper) and Its Treatment with Specific Antiserum, J. Clin. Investigation **14**:373-383 (July) 1935.

test all claims as to the effectiveness of any new therapeutic agent under controlled conditions, it seems especially deplorable to place on the market an untried remedy for a disease as serious as pneumonia. What is worse is the tendency to regard the serum in question as a panacea for all types of pneumococcic pneumonia and to discredit the necessity of typing the pneumococci, a fact which has been laboriously established after twenty-five years of work. Finland and his associates [13] failed to discover any indication that a heterophile antibody has any significance in cases of lobar pneumonia in human beings. They found no constant relationship between the hemolytic titer of the serum and the outcome of the disease. They state: "The claims . . . that are alleged to indicate the superiority of antipneumococcus serum containing heterophile antibody over the unadulterated type-specific antibody may temporarily increase the sale of this material to an ever hopeful and credulous medical public."

Artificial Pneumothorax.—Numerous reports of the favorable effects of induced pneumothorax in the treatment of pneumonia in small groups of patients have appeared during the year. Blake and his associates [14] recommend large initial doses (1,800 cc.) given at the rate of 10 or 15 cc. per minute, followed by refills of smaller amounts, when necessary, at intervals of four or eight hours. Their studies show that when established early in suitable cases, pneumothorax appears to be a useful therapeutic procedure. Their work is summarized in an extensive review.[14b] They believe that the beneficial effect obtained is accounted for by the "lung rest theory," and they suggest that collapse therapy is effective because lobar pneumonia most frequently commences at the hilus and spreads outward. This theory is open to serious question since both Ude [15] and Rigler,[16] whose papers are not mentioned in the review, emphasize the great frequency with which lobar pneumonia commences peripherally. Furthermore, several of the roentgenograms reproduced in Blake's [14b] paper (figs. 6 and 7) show consolidation commencing in the periphery of the lung. Other observers do not regard

13. Finland, M.; Ruegsegger, J. M., and Felton, L. D.: Heterophile Antibodies in Pneumonia, J. Clin. Investigation **14**:683-690 (Sept.) 1935; Should Heterophile Antibody Be Used in Treatment of Pneumococcic Pneumonia? J. A. M. A. **105**: 1180-1182 (Oct. 12) 1935.

14. Blake, F. G.; Howard, M. E., and Hull, W. S.: (*a*) Artificial Pneumothorax in the Treatment of Lobar Pneumonia, J. A. M. A. **105**:1489-1495 (Nov. 9) 1935; (*b*) Artificial Pneumothorax in Lobar Pneumonia, Medicine **15**:1-102 (Feb.) 1936.

15. Ude, W. H.: Roentgenologic Studies in Early Lobar Pneumonia, Am. J. Roentgenol. **26**:691-695 (Nov.) 1931.

16. Rigler, L.: X-Ray Diagnosis of Lobar Pneumonia, in Piersol, G. M.; Bortz, E. L., and others: The Cyclopedia of Medicine, Philadelphia, F. A. Davis Company, 1934, vol. 9, pp. 1072-1077.

this mode of therapy with optimism. Bullowa and Mayer [17] believe that general practitioners will not be justified in employing it until many more carefully controlled studies are made. They regard pneumothorax as a hazardous and unnecessary procedure in cases of the types of lobar pneumonia for which specific antiserums exist. Abernethy and his associates [18] at the Hospital of the Rockefeller Institute studied 6 apparently ideal and carefully controlled cases in which pneumothorax was induced. They concluded that large amounts of air may be introduced without any harm and that pleural pain is often relieved by small amounts but that large amounts frequently cause increased dyspnea, tachypnea, cyanosis and substernal pain, with which statement Bullowa and I concur. Massive amounts given early in the course of the disease according to Blake's technic did not influence the course favorably in 6 cases; there was no reduction of toxicity or apparent shortening of the disease. In 1 patient the pneumonia spread to the other side.

Prophylaxis.—Lister and his associates [19] have published the results of a twenty-four year study of the prophylaxis of pneumonia in native miners in South Africa. They again point out that pneumonia is composed of a group of specific disease entities. Before 1926 pneumonia was caused chiefly by pneumococci, but since that time pneumonia caused by streptococci, staphylococci and Bacillus influenzae has become more prevalent. It seems that prior to 1926 the use of pneumococcus vaccine distinctly lowered the incidence of the disease until the appearance of other organisms as etiologic agents. The increase of the morbidity and mortality rate caused by these organisms led to the addition of streptococci, staphylococci and influenza bacilli to the vaccine. These antigens were used not so much to prevent infection of the respiratory tract, which the authors believe to be initiated by a virus, as to prevent superimposed pulmonary infection caused by these organisms. Although the final figures in the study speak well for the effectiveness of such vaccines in lowering the morbidity rate, they are not completely convincing. Unfortunately, as the authors admit, the alternate method of vaccinating every other man in a given group to evaluate the effectiveness of a vaccine was not practiced. Instead, the results observed in certain groups of vaccinated miners were compared with those in

17. Bullowa, J. G. M., and Mayer, E.: The Hazards of the Induction of Pneumothorax in the Treatment of Lobar Pneumonia, J. A. M. A. **105**:191-193 (July 20) 1935. Bullowa, J. G. M.: Pneumothorax in Pneumonia: An Appraisal, New York State J. Med. **35**:1001-1018 (Oct. 15) 1935.

18. Abernethy, T. J.; Horsfall, F. L., and MacLeod, C. M.: Pneumothorax Therapy in Lobar Pneumonia, Bull. Johns Hopkins Hosp. **58**:35-58 (Jan.) 1936.

19. Lister, S.; Ordman, D., and Peall, P. A.: The Epidemiology of Pneumonia on the Witwatersrand Goldfields and the Prevention of Pneumonia and Other Allied Acute Respiratory Diseases in Native Labourers in South Africa by Means of Vaccine, Pub. South African Inst. M. Research **7**:1-124 (April) 1935.

groups of unvaccinated workers from different mines. Conclusions must therefore be drawn with caution, since, as the authors state on page 30: "One of the most remarkable features of pneumonia on the Witwatersrand is its unequal occurrence from mine to mine."

Ross [20] found that the oral ingestion of types I, II and III pneumococcus vaccines caused protective antibodies to appear in from 60 to 75 per cent of persons. No specific agglutinins were demonstrable. Similar protective antibodies occurred naturally in from 10 to 50 per cent of unvaccinated persons. Finland and Ruegsegger [21] succeeded in producing antibodies in high titer in patients who received subcutaneous injections of 1 mg. of the type-specific carbohydrate of pneumococci of type VIII. The carbohydrate of type III organisms was less effective. Cross-immune reactions between the two related types occasionally occurred.

Nephritis in Pneumonia.—Numerous observers in the past have noted the relative infrequency of nephritis during pneumonia.[22] Transient albuminuria frequently occurred, and renal changes of a degenerative nature were commonly noted. Many observers, including myself, have never encountered clinical nephritis associated with pneumococcic lobar pneumonia. Interest in the matter was renewed since the publication of the studies of Blackman and Rake made several years ago. These authors noted acute nephritis in 9 per cent of children who died from pneumococcic infection but failed to observe it in adults. Seegal [23] recently studied 7 patients with acute nephritis among 1,004 adults with pneumococcic pneumonia, an incidence of 0.7 per cent. The nephritis developed in from two to three weeks after the onset of pneumonia.

Pneumococcic Peritonitis.—Several studies of pneumococcic peritonitis have appeared during the year. King,[24] Tompkins [25] and Drachter [26] report several cases of pelvic infection in women caused by

20. Ross, V.: Human Immunization Against Pneumococcus, J. Immunol. **27**: 307-314 (Sept.) 1934.

21. Finland, M., and Ruegsegger, J. M.: Immunization of Human Subjects with the Specific Carbohydrates of Type III and the Related Type VIII Pneumococcus, J. Clin. Investigation **14**:829-832 (Nov.) 1935.

22. Reimann, H. A.: Acute Lobar Pneumonia, in Piersol, G. M.; Bortz, E. L., and others: The Cyclopedia of Medicine, Philadelphia, F. A. Davis Company, 1934, vol. 9, p. 1059.

23. Seegal, D.: Acute Glomerulonephritis Following Pneumococcic Lobar Pneumonia: Analysis of Seven Cases, Arch. Int. Med. **56**:912-919 (Nov.) 1935.

24. King, J. E.: Pneumococcus Pelvic Infection in Adults, Am. J. Obst. & Gynec. **29**:341-349, 1935.

25. Tompkins, P.: Pneumococcus Pelvic Infection in Women, Am. J. Obst. & Gynec. **31**:70-78 (Jan.) 1936.

26. Drachter, R.: Pneumokokkenperitonitis, Ztschr. f. ärztl. Fortbild. **32**:620-625, 1935.

pneumococci and mention a number of other cases reported in the literature. Although most observers have considered the genital tract as the most frequent source or path of infection, these authors feel that many cases are preceded by acute disease of the respiratory tract which permits entry of pneumococci into the blood stream. The prognosis is good when the infection is localized in the pelvis and can be surgically drained. The prognosis is unfavorable when general peritonitis exists. Adequate drainage appears to offer the only hope for recovery. King and Tompkins believe that the respiratory tract is the portal of entry of infection and this view is substantiated by Schaanning's [27] study. Of 56 cases of pneumococcic peritonitis, in 16 the condition was preceded by pneumonia, in 7 by sore throat and in 2 by otitis media. In only 4 instances did the infection appear to originate from the pelvic organs. In the few cases in which the pneumococci were typed, type I was found seven times and types II, III and IV once each. The mortality rate among 35 children was 31 per cent. All of 14 adult patients died. It appeared that operation in the acute stage was unwise, since the mortality rate was 73 per cent, whereas the rate with expectant treatment was 31.6 per cent. Kramár [28] suggests that pneumococcic peritonitis is more common in children than is generally believed and cited 2 of his own "abortive cases." Many cases probably occur, but recovery follows without the diagnosis of the condition. In many cases the condition is probably regarded as due to simple digestive disturbances. The diagnosis can be made only by abdominal paracentesis and bacteriologic examination of the exudate.

Pneumococcus Toxin.—Petith [29] recently summarized the literaure concerning toxins of the pneumococcus. He points out the complexity of the problem and the divergence of opinion. It has not been possible as yet to determine the rôle played by any of the described substances in actual infection. More studies have recently been made. In one [30] it was shown that small doses of the toxin obtained from autolysates of pneumococci grown anaerobically kill mice. It was possible to prepare an antitoxin against this substance. Coca [31] also reported a toxin pro-

27. Schaanning, C. K.: Ueber Pneumokokkenperitonitis, Acta chir. Scandinav. **77**:256-270 (Nov. 15) 1935.

28. Kramár, J.: Ueber die abortive Form der Pneumokokkenperitonitis, Monatschr. f. Kinderh. **61**:370-373 (March 15) 1935.

29. Petith, H.: Eine kritische Studie über die Rolle der Pneumokokkentoxine im immunbiologischen Bilde der Pneumokokkenerkrankungen, Zentralbl. f. inn. Med. **55**:97-118 (Feb. 3) 1934.

30. Weld, J. T., and Gunther, A.: Effect of Anaerobically Prepared Pneumococcus Autolysate Toxin on Mice and Evaluation of Pneumococcus Autolysate Antitoxin in Mice, J. Exper. Med. **62**:119-127 (July) 1935.

31. Coca, A. F.: A Study of the Pneumococcus Toxins, J. Immunol. **30**:1-32 (Jan.) 1936.

duced by the growth of pneumococci under certain atmospheric conditions. That toxin likewise was antigenic, but it was not composed of the specific polysaccharide. Subcutaneous injections of the toxin often caused high fever, anorexia, local swelling and discomfort. Immunity developed in children after a single injection of the toxin. The toxin could be neutralized by the serum of an immunized child but not by normal serum. About 95 per cent of patients convalescent from pneumonia showed negative results of skin tests when the toxic filtrate was injected. The toxin appeared to be type specific. For example, a person immunized with toxin produced from type I pneumococci reacted weakly to type I toxic filtrate but strongly to the filtrate obtained from other types. These observations, if they can be confirmed, are obviously of considerable significance.

INFLUENZA

The knowledge gained from the highly important investigations on influenza discussed in several previous reviews [32] has been extended by a number of interesting studies. Francis and Magill [33] have found that the rabbit, which is apparently not susceptible to infection after inoculation with the virus of influenza, nevertheless shows specific antibodies in the serum which serve to protect mice against intranasal infection with the virus. Subcutaneous or intraperitoneal injection of the virus into mice also fails to produce symptoms of infection in these animals, but mice so treated are actively immunized against subsequent infection by the intranasal route, which otherwise causes disease. Strains of influenza virus obtained from patients in widely separated groups were found to be immunologically related to each other but were not identical with the virus of swine influenza. The same investigators [34] vaccinated 10 persons subcutaneously with virus grown in tissue culture. No constitutional symptoms were noted. The procedure caused the development or increase of specific protective substance in 9 of the subjects. Several reports [35] of the cultivation of the virus in vitro

32. Klotz, O., and Holman, W. L.: Studies on Influenza, Am. J. M. Sc. **191**: 426-446 (March) 1936. Reimann, H. A.: Infectious Diseases: Review of the Current Literature, Arch. Int. Med. **56**:382-411 (Aug.) 1935. Francis, T.: Recent Advances in the Study of Influenza, J. A. M. A. **105**:251-254 (July 27) 1935.

33. Francis, T., and Magill, T. P.: Immunological Studies with the Virus of Influenza, J. Exper. Med. **62**:505-517 (Oct.) 1935.

34. Francis, T., and Magill, T. P.: Vaccination of Human Subjects with Virus of Human Influenza, Proc. Soc. Exper. Biol. & Med. **33**:604-606 (Jan.) 1936.

35. Francis, T., and Magill, T. P.: Cultivation of Human Influenza Virus in an Artificial Medium, Science **82**:353-354 (Oct. 11) 1935. Smith, W.: Cultivation of the Virus of Influenza, Brit. J. Exper. Path. **16**:508-512 (Dec.) 1935.

have appeared. The virus was isolated during an epidemic of influenza in Australia by Burnet.[36]

Andrewes, Laidlaw and Smith[37] in further studies showed that mice, contrary to expectations, could not be infected directly with washings from the throats of patients with influenza. Before mice could be infected the strains had to be passed through several ferrets. The authors found that the majority of normal persons possess neutralizing antibodies against influenza virus in their blood. They were unable to infect 2 human volunteers with ferret passage virus. The serum of each subject, however, contained neutralizing antibodies before the test was made. The size of the virus particles was estimated by filtration methods to be somewhat smaller than that of the viruses of vaccinia and herpes.[38] The minuteness renders it unlikely that the virus represents a small form of influenza bacillus or of any other bacterium which has been suggested as the causative agent of influenza. These authors, contrary to the experience of Noble and Brainard,[39] were unable to obtain a virus from patients with the common cold.

Dochez and his associates[40] inoculated human volunteers with the bacteria-free filtrate of nasopharyngeal washings from patients with influenza both of the epidemic and of the sporadic type. The type of infection evoked with virus from the sporadic type resembled the syndrome of the common cold rather than that of influenza. It was noted, however, that a more pronounced constitutional reaction occurred after inoculation with influenza virus than after inoculation with virus of the common cold. Volunteers were successfully inoculated with the virus after its cultivation in vitro. The presence of certain pathogenic bacteria commonly found in the upper respiratory tract was not observed to modify the character of the induced infection. The difficulty of differentiating the virus of the common cold from that of influenza was pointed out. The two viruses were thought to be closely related biologically.

---

36. Burnet, F. M.: Influenza Virus Isolated from Australian Epidemic, M. J. Australia **2**:651-653 (Nov. 9) 1935.

37. Andrewes, C. H.; Laidlaw, P. P., and Smith, W.: Influenza: Observations on the Recovery of Virus from Man and on the Antibody Content of Human Sera, Brit. J. Exper. Path. **16**:566-582 (Dec.) 1935.

38. Elford, W. J.; Andrewes, C. H., and Tung, F. F.: The Sizes of the Viruses of Human and Swine Influenza as Determined by Ultrafiltration, Brit. J. Exper. Path. **17**:51-53 (Feb.) 1936.

39. Noble, W. C., and Brainard, D. H.: Note on Susceptibility of Ferrets to Virus of Common Cold, J. Bact. **29**:407-411 (April) 1935.

40. Dochez, A. R.; Mills, K. C., and Kneeland, Y.: Studies on the Virus of Influenza, J. Exper. Med. **63**:581-598 (April) 1936.

Brightman,[41] in studies involving the infection of ferrets with influenza virus obtained from children, noted the invasion of the lungs by hemolytic streptococci in about a third of his animals. The streptococci evidently originated in the ferret, since immunologically similar strains were found in normal ferrets. They seemed to be a secondary invader affecting animals after the resistance had been reduced by the influenza virus infection.

THE COMMON COLD

Dochez and his associates [42] report new observations on the bacteria-free filtrable virus of the common cold. They succeeded in cultivating the virus in a tissue culture medium, and they reproduced the disease in volunteers inoculated with this culture virus. Interesting observations were made concerning the presence of inclusion bodies in the epithelial cells of the upper respiratory tract in human beings.[43] These inclusion bodies were found more commonly in persons with a mild respiratory infection. The histologic structure and staining properties of the cytoplasmic inclusions, the authors believe, differentiate them from cell detritus or other artefacts. It is claimed that the inclusion bodies have been cultivated in tissues of the chick embryo.

At a recent meeting Kerr [44] stated that it does not seem necessary to assume that a virus plays any part in causing the common cold. Many patients with a "cold" do not show symptoms characteristic of infection. He believes that environmental changes, such as chilling, irritants and various vasomotor disturbances, cause the symptoms regarded as those of the common cold. He raises the question as to whether or not products of tissue culture other than a virus may not in themselves cause symtoms. I do not concur in this extreme view of Kerr. Beyond question symptoms of rhinitis may be produced by environmental changes, by various irritants and by other causes, but from clinical and epidemiologic observation and carefully controlled experiments it is well established that certain forms of the ill defined complex known as the common cold are definitely infectious and are caused by a transmissible virus. The few experiments cited by Kerr which resulted in failure to transmit the disease cannot be said to prove the noninfectious nature of the illness.

---

41. Brightman, I. J.: Streptococcus Infection Occurring in Ferrets Inoculated with Human Influenza Virus, Yale J. Biol. & Med. **8**:127-135 (Dec.) 1935.

42. Dochez, A. R.; Mills, K. C., and Kneeland, Y.: Studies on the Common Cold, J. Exper. Med. **63**:559-579 (April) 1936.

43. Broadhurst, J.; Liming, R. M.; MacLean, M. E., and Taylor, I.: Cytoplasmic Inclusion Bodies in the Human Throat, J. Infect. Dis. **58**:134-149 (March-April) 1936.

44. Kerr, W. J.: The Common Cold, J. A. M. A. **107**:323 (Aug. 1) 1936.

During the past year two papers [45] have appeared concerning the use of "heterophile" antigen vaccine to be given by mouth for the prevention of colds. The vaccine contains pneumococci, influenza bacilli, streptococci and Micrococcus catarrhalis. In the face of much excellent evidence that the cold is caused by a filtrable virus, environmental changes and various other causes, it is difficult to understand the persistence of investigators in ignoring modern research in this regard. It is now generally believed that pneumococci or other organisms commonly found in the rhinopharynx may at times be responsible only for certain complications or sequelae of the cold. Furthermore, no one has as yet produced a vaccine for the common cold which is effective even when given by the subcutaneous route, which is the usual method of stimulating antibodies. Evidence that immunity is established when any vaccine is taken by mouth is vague even in the case of typhoid vaccine, which is highly effective when given subcutaneously. Furthermore, the statistical evidence used by the authors to demonstrate the effectiveness of oral heterophile vaccine is insufficiently controlled, too limited and unconvincing.[46]

ACUTE RHEUMATIC FEVER

Coburn and Pauli [47a] studied a group of children with rheumatic heart disease among whom occurred an epidemic of influenza complicated with Streptococcus haemolyticus infections. They believe that the influenza virus had no effect in reactivating rheumatic fever, but recrudescences occurred after the development of postinfluenzal streptococcic infections due to a single strong toxin-producing strain of Str. haemolyticus. None of the 7 children who escaped streptococcic infection showed rheumatic symptoms; 14 of the 17 who were infected suffered a relapse of rheumatic fever. In another study [47b] they found a close relationship between streptococci causing scarlet fever and those causing rheumatic fever as regards the production of toxin and streptolysin. Neither active nor passive immunization to hemolytic streptococci was found to inhibit the development of rheumatic infection. These observations suggested to the authors that the immune response of the

45. Rockwell, G. E.; Van Kirk, H. C., and Powell, H. M.: Oral Immunization to Colds, J. Immunol. **28**:475-484 (June) 1935; Further Studies on Oral Immunization to Colds, Science **82**:177-178 (Aug. 23) 1935.

46. Thomson, D.; Thomson, R., and Thompson, E. T.: Immunization by the Oral Route in Respiratory Infections, Brit. M. J. **1**:258-261 (Feb. 8) 1936. Rockwell, Van Kirk and Powell.[45]

47. Coburn, A. F., and Pauli, R. H.: Studies on the Immune Response of the Rheumatic Subject and Its Relationship to Activity of the Rheumatic Process, (*a*) J. Exper. Med. **62**:129-136, 137-158 and 159-169 (Aug.) 1935; (*b*) J. Clin. Investigation **14**:755-762, 763-768, 769-781 and 783-791 (Nov.) 1935.

host plays an important rôle in the development of the disease. Infection with certain streptococci initiates a process peculiar to rheumatic subjects; that is, a substance which alters mesodermal tissues is released when an immune response to the streptococci occurs.

While these studies and many previous ones have incriminated infections caused by hemolytic streptococci in inciting a relapse of rheumatic fever, recent observations [48] show that other factors also are of importance. While Bland and Jones admit that infection of the respiratory tract precedes 75 per cent of the observed recurrences, they show that in the remaining 25 per cent there was no preceding infection of the respiratory tract. Furthermore, tonsillitis and pharyngitis were not consistently followed by the recurrence of rheumatic fever in likely subjects. In their experience other forms of infection, injection of antityphoid vaccine, accidents involving fractured bones or sprained joints and surgical operations also have appeared to reactivate a latent rheumatic infection or have raised the asymptomatic phase of rheumatic fever to a clinical level.

The same authors [49] made a study concerning the significance of chorea in rheumatic fever. They point out that although chorea appears to be a manifestation of rheumatic fever, the positive proof of the etiologic relationship is controversial and awaits further study. Over a period of eight years 72 per cent of 482 patients with chorea exhibited other signs of rheumatic fever; in 28 per cent chorea alone was found. Heart disease occurred in 73 per cent of those with both rheumatic fever and chorea but in only 3 per cent of those with chorea alone. Death occurred in 1.7 per cent of patients with chorea alone, as compared with 14 per cent of those with other rheumatic symptoms. Chorea therefore appears to be a mild manifestation of rheumatic disease not often followed by the usual serious consequences.

Two studies [50] confirm the close relationship between rheumatic activity and changes in the sedimentation rate of the blood. Acute chorea prompted only a slight, transient increase. In rheumatic fever the sedimentation rate closely paralleled the activity of the disease and led the authors to regard the test as valuable in following the progress of the disease. An increase in the rate indicated reactivation of the virus

48. Bland, E. F., and Jones, T. D.: Clinical Observations on the Events Preceding the Appearance of Rheumatic Fever, J. Clin. Investigation **14**:633-648 (Sept.) 1935. Edström, G.: Mechanisches Trauma und nachfolgende Febris rheumatica, Acta med. Scandinav. **88**:342-353, 1936.

49. Jones, T. D., and Bland, E. F.: Clinical Significance of Chorea as a Manifestation of Rheumatic Fever, J. A. M. A. **105**:571-577 (Aug. 24) 1935.

50. Payne, W. W., and Schlesinger, B. A.: Study of the Sedimentation Rate in Juvenile Rheumatism, Arch. Dis. Childhood **10**:403 (Dec.) 1935. Wood, P.: The Erythrocyte Sedimentation Rate in Diseases of the Heart, Quart. J. Med. **5**:7 (Jan.) 1936.

or increasing severity of the disease, while a decreasing rate was of good prognostic import. Although the continued activity of the disease is almost always accompanied by an abnormally high rate, I do not believe that an increased rate invariably indicates continuation of the infection. In cases of lobar pneumonia, for example, the sedimentation rate may be increased for weeks after the crisis and may be the last measurable factor to return to normal.

Several studies on the etiology of rheumatic fever have been published recently. Schlesinger and his associates [51] were able to detect particles which resembled the elementary bodies of vaccinia, psittacosis and varicella when rheumatic exudates and suspensions of infected tissues were centrifugated at high speed. These bodies when suspended in suitable fluids were agglutinated specifically by the serums of patients with acute rheumatic infections. No agglutination occurred in serum from patients in whom the infection was quiescent or in serum from normal persons. They suggest that in rheumatic fever the streptococcus causes an infection and prepares the soil, so to speak, for the growth of the virus. Coles [52a] reports the demonstration of similar bodies in acute rheumatic fever and in rheumatoid arthritis but also in 50 per cent of pericardial fluid from patients with other conditions as well. Aschoff [52b] regards the work of Schlesinger as of great significance but believes that the virus is the primary cause of the disease and that the streptococcus is a secondary invader. If Aschoff's view, which is held by many, is correct, it is striking how differently streptococcic infection becomes manifest in rheumatic fever as compared with its behavior as a complication of influenza.

Before regarding these studies too seriously, the recent work of Logrippo [53] must be considered. This investigator, studying the so-called "globoid bodies" of poliomyelitis, found that opalescence and micrococcoid forms developed in culture mediums both with and without the presence of virus. He showed that the establishment of an electrical field caused tissue lipoids to pass into suspension and to react to stains similar to the forms observed in virus culture. The physical state of certain fluids, he believes, can well account for the stable emulsion that

51. Schlesinger, B.; Signy, A. G.; Amies, C. R., and Barnard, J. E.: Aetiology of Acute Rheumatism: Experimental Evidence of a Virus as the Causal Agent, Lancet **1**:1145-1149 (May 18) 1935.

52. (*a*) Coles, A. C.: Virus Bodies in the Pericardial Fluid of Rheumatic Fever and Other Conditions and in Joint Fluid of Rheumatoid Arthritis, Lancet **2**:125-126 (July 20) 1935. (*b*) Aschoff, L.: Ueber den spezifischen infektiösen Rhuematismus, München. med. Wchnschr. **82**:1597-1598 (Oct. 4) 1935.

53. Logrippo, G. A.: Concerning the Nature of the Globoid Bodies, J. Bact. **31**:245-253 (March) 1936.

is being interpreted as growth. Nevertheless, other recent studies [54] have shown that the elementary bodies of vaccinia contain ash, carbohydrate, fat and nitrogen similar to other substances of protoplasmic origin.

UNDULANT FEVER (BRUCELLIASIS, BRUCELLOSIS)

The annual increase in the number of recognized and reported cases of undulant fever since 1924 has led many to regard it as a new and spreading disease.[55] However, as old records are searched descriptions of maladies are found which resemble undulant fever in many respects and make it seem almost certain that the disease has existed in this country for many years. Interpretations of old reports must, however, be accepted with caution, as illustrated by an article on certain aspects of the life of Lincoln.[56] It appears that in 1818 Lincoln's mother, Nancy Hanks, contracted and died from a disease known as "milk-sick" which swept southern Indiana in epidemic form. It was thought at the time that the disease was passed to human beings in cow's milk. Many cows aborted. At present this epidemic is believed by some to have been a variety of undulant fever. There are, however, several factors opposed to this view. Undulant fever seldom occurs in an explosive epidemic, and it is not characterized by a mortality rate as high as that reported in the 1818 outbreak. Recent investigations have confirmed the opinion of the pioneers in regard to snake-root in fodder as the cause of the disease. This herb causes "trembles" in cattle and is often fatal. The poison is transmissible to human beings through the milk.

The publication of numerous clinical descriptions and epidemiologic studies [57] on undulant fever during the past year or two indicate widespread interest in the disease. Reviews of the disease as it appeared in Scotland, England, Sweden and elsewhere have been published and a congress on brucellosis was held in France. Unfortunately, little actual advance in knowledge has been made.

---

54. Hughes, T. P.; Parker, R. F., and Rivers, T. M.: Immunological and Chemical Investigations of Vaccine Virus, J. Exper. Med. **62**:349-352 (Sept.) 1935.

55. Roth, F.: Ueber den Infektionsmodus, die latente Infektion und die Ursache der Häufigkeitszunahme der Bangschen Erkrankung des Menschen, Ztschr. f. klin. Med. **126**:507-534 (April) 1934.

56. Carskadon, T. R.: Mother of Lincoln, Delineator, February 1936, p. 51.

57. Beattie, C. P.; Smith, J., and Tulloch, W. J.: Undulant Fever in Scotland, Lancet **1**:1427-1431 (June 22) 1935. Dalrymple-Champneys, W.: Undulant Fever, with Especial Reference to Its Clinical Aspects in England and Wales, ibid. **2**:1449-1453 (Dec. 28) 1935. Olin, G.: Studies on Undulant Fever in Sweden, Svenska läk.-sällsk. handl. **61**:63-168, 1935. Harris, H. J.: Undulant Fever: Difficulties in Diagnosis and Treatment; Preliminary Report of Fifty-One Cases, New York State J. Med. **34**:1017-1021 (Dec. 1) 1934. The First Reported Case of Undulant Fever, foreign letter, J. A. M. A. **105**:1366 (Oct. 26) 1935.

Many clinical reports have recently appeared describing unusual cases or complications which, while largely new to the medical profession in the United States, were for the most part observed and described years ago by British army surgeons in Malta. Meningitis due to Brucella has been reported in several papers.[58] One patient who recovered was treated with injections of toxic filtrate of cultures of Brucella and by frequent copious drainage of the spinal fluid.[58b] Marietta [58d] collected reports of several cases in which the condition was characterized by meningeal and osseous involvement and added a report of a case of his own. Cases of undulant fever associated with pneumonia as an outstanding feature were reported by Johnson and Bogart.[59] Krohmann [60] reports a case in which hematemesis occurred, which he believes may have resulted from ruptured esophageal varices secondary to hepatic cirrhosis and splenomegaly in a youth of 26. He suggests that prolonged (two years) infection may have caused the cirrhosis. Similar cases are reported by Diehl and Roth.[61] Cases in which cholecystitis and hepatitis also were present are reported in other papers.[62] Spondylitis also has been observed.[63]

Several studies emphasize the prevalence of infection, latent or otherwise, in the population as a whole, as evidenced by the frequency of positive results of serum agglutination and cutaneous tests. It is said that agglutinins and specific cutaneous sensitivity develop only when there has been invasion of tissues by the living brucella organism followed by the actual disease or inapparent, symptomless infection, as discussed in subsequent paragraphs. Heathman [64] studied the agglutinin

58. (*a*) Bingel, A., and Jacobsthal, E.: Meningitis in Alcaligenes Abortus Infection, Klin. Wchnschr. **12**:1093-1095 (July 15) 1933. (*b*) Hartley, J. A., and Millice, G. S.: Undulant Fever Meningitis, J. A. M. A. **103**:251-253 (July 28) 1934. (*c*) Hardy, A. V.; Borts, I. H., and Jordan, C. F.: Undulant Fever in Iowa, Tr. A. Am. Physicians **49**:93-99, 1934. (*d*) Marietta, S. U.: Involvement of the Spinal Meninges and of Bone in Undulant Fever Simulating Tuberculosis, Am. Rev. Tuberc. **32**:257-284 (Sept.) 1935.

59. Johnson, R. M.: Pneumonia in Undulant Fever, Am. J. M. Sc. **189**: 483-487 (April) 1935. Bogart, F. B.: Pulmonary Changes in Undulant Fever, South. M. J. **29**:1-8 (Jan.) 1936.

60. Krohmann, L.: Ein bemerkenswerde Fall von Morbus Bang mit Magendarmblutungen, München. med. Wchnschr. **81**:1268-1269 (Aug. 17) 1934.

61. Diehl, F., and Roth, F.: Hepatolienale Syndrome bei Bangscher Krankheit, Deutsches Arch. f. klin. Med. **178**:271-288, 1935.

62. (*a*) MacQuiddy, E. H., and Martin, J. W.: Cholecystitis Due to Brucella Melitensis, Nebraska M. J. **19**:227 (June) 1934. (*b*) Mettier, S. R., and Kerr, W. J.: Hepatitis and Cholecystitis in the Course of Brucella Infection, Arch. Int. Med. **54**:702-710 (Nov.) 1934.

63. Snyder, C. H.: Spondylitis in Undulant Fever: Report of Two Cases, J. Michigan M. Soc. **34**:224-228 (April) 1935. MacQuiddy and Martin.[62a]

64. Heathman, L. S.: A Survey of Workers in Packing Plants for Evidence of Brucella Infection, J. Infect. Dis. **55**:243-265 (Nov.-Dec.) 1934.

and dermal reactions of employees in meat packing plants. She found a divergence in the incidence of the allergic state and the presence of agglutinins. Eighty per cent of the employees in contact with fresh blood and tissues showed allergic responses in contrast with 55 per cent in the group as a whole. Only 8.4 per cent of all the employees showed significant agglutinins, a figure close to that noted by other investigators. Agglutinins were present in about the same percentage of workers exposed to fresh tissues as of those not exposed to infection. The high percentage of persons in the allergic state indicated that the cutaneous test as a diagnostic aid must be used with caution, especially when the results of the agglutination test and blood cultures are negative. Heathman's results seemed to show that the high incidence of positive cutaneous reactions of those most exposed to fresh blood and tissues may be the result of numerous and repeated exposures to Brucella, which perhaps caused symptomless or subclinical infection. Workers handling beef are almost constantly exposed to infection but rarely show symptoms of clinical infection, whereas among the pork handlers exposure is less frequent but when it occurs infection more often reaches the clinical stage. The author believes that the agglutination and cutaneous reactions alone are not reliable criteria of the degree of infection. Conversely, other observers have noted that from 10 to 16 per cent of the patients with undulant fever fail to have agglutinins. Goldstein [65] recommends the cutaneous test only as a supplementary diagnostic procedure. Favorite and Culp [66] present more evidence to show that the intradermal test is specific.

As remarked in a preceding paragraph, many studies indicate the widespread nature of the disease.[67] Evidences of previous infection, as registered by the presence of agglutinins and a positive result of the cutaneous test in an otherwise healthy person, are frequently noted in persons with no history of infection with Brucella. It appears, then, that while a large portion of the population are repeatedly exposed to infection with Brucella, a certain proportion are apparently resistant to infection or receive subinfective doses while others, with less resistance, show signs and symptoms of the disease in widely divergent gradations. Some, although actually infected (symptomless infection, as evidenced by the presence of agglutinins and cutaneous sensitivity), never show signs or symptoms; some show symptoms so mild as to be unrecog-

---

65. Goldstein, J. D.: Cutaneous Reactions in the Diagnosis of Undulant Fever, J. Clin. Investigation **13**:209-218 (March) 1934.

66. Favorite, G. O., and Culp, C. F.: The Intradermal Test in Undulant Fever, J. Lab. & Clin. Med. **20**:522-526 (Feb.) 1935.

67. (*a*) Evans, A. E.: Chronic Brucellosis, J. A. M. A. **103**:665-667 (Sept. 1) 1934. (*b*) Scoville, W. F.: The Prevalence of Mild Brucella Abortus Infections, ibid. **105**:1976-1977 (Dec. 14) 1935. Roth.[55]

nizable clinically; some manifest typical signs and symptoms which comprise the typical clinical entity of undulant fever, and a few apparently have little or no resistance and rapidly succumb to overwhelming infection. There is no evidence to show that virulence per se of the infecting micro-organism is responsible for the variations in the degree of severity of the illness; the greatest variable seems to involve the host, the macro-organism (Meyer [68]). These views are illustrated in reports of epidemics in two institutions. In both the source of the contaminated milk was known. In one study [69] of 300 elderly inmates, all whom undoubtedly ingested the contaminated milk, 35 per cent of those tested gave evidence of symptomless infection by the presence of specific serum agglutinins, but only 14 actually showed symptoms which lasted for from four to forty weeks. Three of the patients died. The other report [70] concerns an epidemic among 210 children, all of whom drank milk infected with Brucella melitensis, variety suis, in which only 14 per cent of those tested showed agglutinins for this organism, only 13 per cent showed positive cutaneous reactions and only 2 showed manifestations of the disease. When the contaminated milk was withdrawn the agglutinins disappeared rapidly, but the cutaneous reaction was strongly positive and in some cases continued to be positive.

Two papers deal especially with low grade, often afebrile undulant fever. Because a certain number of patients with mild but prolonged infection with Brucella (chronic brucellosis) complain of exhaustion, insomnia, irritability and aches and pains for which no objective signs can be found, they are apt to be regarded as neurasthenic or neurotic. Evans [67a] suggests that patients with such a train of vague symptoms should always be tested for the presence of agglutinins and the cutaneous reaction to Brucella. Since both these tests are often unreliable, efforts should be made to cultivate the organism from the blood or excretions, a procedure admittedly difficult and unlikely to be successful in cases of low grade infection. Exception may be taken to Evan's conclusion that "clinical diagnosis is extremely difficult even in severe cases." Undulant fever in my experience has been relatively easy to detect, especially when sought for. The symptoms, signs and laboratory findings in the average case are usually characteristic.

Scoville [67b] records his own case in which the condition was characterized by a prolonged afebrile course. The condition was considered as due to neurasthenia or chronic neutropenia until proved to

68. Meyer, K. F.: Latent Infections, J. Bact. **31**:109-135 (Feb.) 1936.

69. Horning, B. G.: Outbreak of Undulant Fever Due to Brucella Suis, J. A. M. A. **105**:1978-1979 (Dec. 14) 1935.

70. McBryde, A.; Daniel, N. C., and Poston, M. A.: Brucella Infection in Children, J. Pediat. **4**:401-405 (March) 1934.

be undulant fever after five months, when the result of a cutaneous test was found to be strongly positive. Agglutinins were absent. Of interest also is the record of a normal sedimentation rate of the erythrocytes. This is contrary to what is typical of most infections, and it appears to be a characteristic peculiar to undulant fever, as pointed out by Curschmann.[71]

The treatment of undulant fever is dealt with in a comprehensive review.[72] The authors conclude that a successful method still awaits development. No therapeutic agent has as yet been found which has been proved to alter to a significant degree the natural course of the disease. They believe that the beneficial effects accruing from whatever therapy is used are due to nonspecific systemic reactions, an opinion in which I concur. The surprisingly few studies of the influence of specific immune serum therapy in experimentally infected animals have not been encouraging.[73]

Several experimental studies are of interest. Feldman[74] detected agglutinins in 10 per cent of 500 dogs but was unable to cultivate Brucella from any. Attempts[75] to convert bovine strains into porcine strains by passage of bovine strains of Brucella through hogs were unsuccessful.[75] The Brucella are pathogenic for white mice.[76]

A general review of the pathology of undulant fever was published by Sharp.[77] Wight[78] discusses the program for a nation wide campaign to control the disease in cattle. It is proposed to slaughter all cattle with specific agglutinins in the serum. Thus far it is estimated that about $25 a head will be paid for the animals destroyed.

---

71. Curschmann, H.: Ueber die diagnostische Bedeutung der Senkungsreaktion bei akuten Infektionskrankheiten, München. med. Wchnschr. **80**:1767-1768 (Nov. 10) 1933.

72. Carpenter, C. M., and Boak, R. A.: The Treatment of Human Brucellosis: A Review of Current Therapeutic Methods, Medicine **15**:103-127 (Feb.) 1936.

73. Gwatkin, R.: Brucella Abortus Infection in Guinea Pigs: Prevention and Treatment with Immune Serum, J. Infect. Dis. **53**:230-236 (Sept.-Oct.) 1933. Beach, B. A.: The Influence of Bovine Serum on Brucella Infections in Guinea Pigs, ibid. **56**:38-40 (Jan.-Feb.) 1935.

74. Feldman, W. H.; Mann, F. C., and Olson, C.: The Spontaneous Occurrence of Brucella Agglutinins in Dogs, J. Infect. Dis. **56**:55-63 (Jan.-Feb.) 1935.

75. Gilman, H. L.; Milks, C. H., and Birch, R. R.: Passage of Bovine Brucella Through Swine, J. Infect. Dis. **54**:171-174, 1934.

76. Singer, C., and Shaw, E. B.: J. Bact. **29**:44 (Jan.) 1935. Feldman, W. H., and Olson, C.: The Pathogenicity of Brucella Abortus for White Mice, J. Infect. Dis. **57**:212-222 (Sept.-Oct.) 1935.

77. Sharp, W. B.: Pathology of Undulant Fever, Arch. Path. **18**:72-108 (July) 1934.

78. Wight, A. E.: The Nationwide Campaign to Control Bang's Disease, J. Am. Vet. M. A. **87**:291-295 (Sept.) 1935.

TUBERCULOSIS

A number of important experimental studies of tuberculosis have been made. Derick, Branch and Crane [79] found it difficult to diminish in animals the hypersensitivity to tubercle bacilli. The best method employed a heat-killed vaccine. The life of infected animals was prolonged after the use of such an antigen. In the course of their work the investigators tested their own sensitivity to tuberculin. One who had had tuberculosis failed to react, while another who had never had active tuberculosis reacted vigorously. The experience made them doubtful of the clinical value of the tuberculin test as regards diagnostic problems in individual cases, a feeling which I share. The frequency with which the reaction is negative in clinically proved cases of tuberculosis and positive when active tuberculosis cannot be demonstrated renders the test as reliable or as unreliable as any other test of this kind. The test is no doubt valuable when applied to large numbers of supposedly healthy persons for the purpose of detecting cases of subclinical transmissible tuberculosis.

Oppenheimer [80] produced a lesion which was similar to that of so-called epituberculosis (benign, resolving preliminary tuberculosis of childhood) by introducing dead tubercle bacilli intratracheally into hypersensitive rabbits. When living bacilli were injected, progressive tuberculosis developed. It was suggested that epituberculosis is caused by the erosion of a bronchus by a caseous lymph node which liberates tuberculoprotein and dead bacilli into the lungs of sensitized and immunized persons.

Clawson [81a] studied the relation of allergy to the presence of lesions in animals vaccinated with BCG. He found that in animals made allergic and subsequently inoculated with living or heat-killed BCG extensive tuberculosis developed. Normal animals inoculated with BCG rarely showed pathologic changes. It appeared that the allergic state caused a marked increase in the susceptibility to the development of lesions. The experiments further supported the belief that no allergy exists without tuberculous lesions.

---

79. Derick, C. L.; Branch, E. A. G., and Crane, M. P.: Attempts to "Desensitize" Tuberculous Guinea Pigs with Dead Vaccine and Products of Tubercle Bacillus, Am. Rev. Tuberc. **32**:218-228 (Aug.) 1935.

80. Oppenheimer, E. H.: Experimental Studies on the Pathogenesis of Epituberculosis, Bull. Johns Hopkins Hosp. **57**:247-276 (Nov.) 1935.

81. Clawson, B. J.: (*a*) Relation of Allergy and Lesions in Animals Vaccinated with B C G, Arch. Path. **19**:673-678 (May) 1935; (*b*) Experiments Relative to Vaccination Against Tuberculosis with the Calmette-Guérin Bacillus (B C G), ibid. **20**:343-368 (Sept.) 1935; (*c*) Destruction of Tubercle Bacilli Within Phagocytes in Vitro, J. Infect. Dis. **58**:64-69 (Jan.-Feb.) 1936.

The same investigator [81b] noted that guinea-pigs and rabbits vaccinated with BCG were protected against infection with strains of virulent tubercle bacilli. Both subcutaneous and intravenous injections of living or heat-killed BCG organisms were found to be efficacious. The injection of living organisms intravenously is not considered a safe method, however. Allergic reactions were produced in sensitive animals. Animals vaccinated intravenously with heat-killed organisms did not become allergic. Clawson does not believe that allergy which develops in the course of subcutaneous vaccination is especially harmful or dangerous. In another paper Clawson [81c] reports on the demonstration in vitro of lysis of tubercle bacilli in the presence of immune serum. Lysis occurred much more slowly in normal serum. Mononuclear leukocytes of immune and allergic animals when washed free from serum appeared to be more effective in bringing about lysis than normal leukocytes. From these observations it is suggested that lysis of tubercle bacilli is probably a natural method of combating and destroying the organisms in a tuberculosis-infected body, yet Krause in 1926 presented experimental evidence which weighed against any interpretation which would make immunolyses decisively responsible for the results observed.

Scheel,[82] of Oslo, reports that the morbidity among students working with tuberculous patients is higher than that among the general population. His studies indicated that students with negative results of cutaneous tests showed a morbidity three times as high as that shown by those with positive results of cutaneous tests. BCG vaccine is said to have greatly reduced the morbidity rate among students with negative results of cutaneous tests. These views are at variance with many recent studies which purport the existence of hypersensitivity or allergy to render the liability to reinfection greater. I believe that the dangers of allergy as a liability to tuberculosis in the human subject have been exaggerated.

Smithburn,[83] studying the morphology of colonies of tubercle bacilli, concluded that virulence is associated usually with the number of organisms present and with the proportion of S types in the culture. Not all S forms are virulent. He believes that the native resistance of the rabbit is associated with a power to dissociate inoculated S bacilli into rough (R) forms and then destroy them. This power is not possessed by the naturally susceptible guinea-pig. I am skeptical whether rabbits actually possess a "power" to enforce dissociation. Many other observers have failed to demonstrate any connection between microbic dis-

82. Prevention of Tuberculosis in Medical Students with BCG Vaccine, foreign letter, J. A. M. A. **105**:1925 (Dec. 7) 1935.

83. Smithburn, K. C.: The Colony Morphology of Tubercle Bacilli, J. Exper. Med. **62**:645-663 (Nov.) 1935.

sociation and recovery from infection. Smithburn's observations may, however, be the first to demonstrate the occurrence. Besta,[84] in studying the same problem, was unable to detect the profound biologic changes between the S and the R forms of tubercule bacilli, such as are noted among certain other bacteria.

Studies [85] have been made on the waxes of tubercle and leprosy bacilli. The unsaponifiable fractions of these organisms, though extremely stable chemical compounds and insoluble in water, are remarkable stimulants of cells. They give rise to the production of new monocytes which fuse into giant cells, surround the wax and engulf it. The waxes are then slowly disintegrated without damage to the cells. They have no effect on the resistance of the host.

An excellent series of studies showing the importance of familial infections and the danger of infection to those exposed to tuberculosis has been published by Opie and his associates.[86] Opie [87] also summarizes the present concepts of tuberculous infection and disease. Michelson [88] reviews the literature concerning the primary complex of tuberculosis of the skin and adds 2 case reports of his own.

MENINGITIS

Numerous outbreaks of localized epidemics of meningococcic meningitis during the past year have prompted the publication of several pertinent studies. Neal [89] points out the frequency of the disease in infants under 1 year of age and the difficulties of diagnosis unless the spinal fluid is examined or blood cultures are made. She advises conservatism in serum therapy and recommends the injection of 20 cc. of serum intraspinally once in twenty-four hours after drainage of the subarachnoid space. Spinal drainage should be repeated at intervals of from twenty-four to forty-eight hours to relieve pressure. Tillett and Brown [90] studied a series of 21 cases, in which there was only 1

84. Besta, B.: Untersuchungen über die "Dissoziation" von Tuberkelbacillen, Ztschr. f. Hyg. u. Infektionskr. **117**:403-425 (Nov.) 1935.

85. Sabin, F. R.; Smithburn, K. C., and Thomas, R. M.: Cellular Reactions to Waxlike Materials from Acid Fast Bacteria, J. Exper. Med. **62**:751-769 and 771-786 (Dec.) 1935.

86. Opie, E. L.: Present Concepts of Tuberculous Infection and Disease, Am. Rev. Tuberc. **32**:617-630 (Dec.) 1935.

87. Opie, E. L., and McPhedran, F. M.: Organization of Out-Patient Tuberculosis Clinic for Epidemiological Investigation, Am. J. Hyg. **22**:539-658 (Nov.) 1935.

88. Michelson, H. E.: The Primary Complex of Tuberculosis of the Skin, Arch. Dermat. & Syph. **32**:589-601 (Oct.) 1935.

89. Neal, J. B.: Meningococcic Meningitis in Children, J. A. M. A. **105**:568-571 (Aug. 24) 1935.

90. Tillett, W. S., and Brown, T. M.: Epidemic Meningococcus Meningitis, Bull. Johns Hopkins Hosp. **57**:297-316 (Nov.) 1935.

death. All the patients received serotherapy intravenously and intraspinally. The authors emphasize the value of spinal drainage in itself. The low mortality rate in this series is in striking contrast with that reported by Tripoli [91] (65 per cent of 221 cases). Tripoli points out how unsatisfactory therapeusis of bacterial meningitis is in general. In a study of 468 cases, classified etiologically, the mortality rate from meningitis caused by bacteria other than meningococci was 98 per cent. I am of the opinion that the mortality rate would be considerably lower if spinal puncture and examination of the spinal fluid were made and reported in every case of suspected meningitis. Conklin [92] discusses the difficulties of making diagnoses in cases of atypical meningococcic infection without meningeal involvement.

In classifying cases of meningitis the diagnosis should be confirmed by cultural and serologic methods. In forms other than tuberculous meningitis or meningitis due to Torula, morphologic identification by stained preparations is unreliable and insufficient. Cocci ordinarily gram-positive may, if dead, be decolorized. Two cases of meningitis said to have been due to the pneumococcus in which a cure was obtained are reported,[93] but the diagnosis was based only on examination of slides of stained preparations. Reports of this kind are unacceptable and misleading. Without bacteriologic studies of the solubility in bile and a determination of the type, the pneumococcus often cannot be differentiated from certain other gram-positive cocci.

A method by which meningococcic meningitis can be diagnosed quickly is urgently needed. It is common practice to administer antimeningococcus serum as soon as gram-negative cocci are found in stained smears of spinal fluid, which is perhaps justifiable considering the imperfection of tests in current use. Much serum is no doubt wasted, and perhaps some harm is done, since other coccic invaders of the meninges may be gram-negative. It is not possible to identify bacteria with certainty on the basis of morphologic or tinctorial characteristics alone. Furthermore, the type-specificity among meningococci renders the use of homologous type-specific therapy imperative. Since positive identification by cultural methods is too time consuming, it is hoped that some test like the precipitin reaction, as proposed by Rake,[94]

91. Tripoli, C. J.: Bacterial Meningitis, J. A. M. A. **106**:171-175 (Jan. 18) 1936.

92. Conklin, C. B.: Meningococcemia, M. Ann. District of Columbia **4**:313-315 (Dec.) 1935.

93. Meyer, P. R.: Pneumococcic Meningitis, J. A. M. A. **105**:1844-1845 (Dec. 7) 1935. Smith, H. R.: Pneumococcic Cerebrospinal Meningitis with Recovery, ibid. **105**:1845 (Dec. 7) 1935.

94. Rake, G.: Studies on Meningococcus Infection, J. Exper. Med. **58**:375-383 (Sept.) 1933.

will solve the problem. He [95] recently discussed the problem in the epidemiology of type-specific meningococci.

Scott, Rivers and Armstrong [96] studied cases of bacteria-free acute lymphocytic choriomeningitis in which a virus was recovered from the spinal fluid. Although the patients had no contact with one another, the viruses were found to be identical or closely related. In last year's review [97] these results were shown to be open to some criticism on the basis of the work done by Traub, who found a similar virus in mice which he said he believed was the natural host or source of the virus. The recent studies by Rivers and Scott, however, definitely demonstrate that the virus isolated by them was derived from the patient's spinal fluid. It was immunologically identical with the virus of Armstrong and Lillie and with that of Traub. In regard to diagnosis, they point out the confusing fact that signs of meningitis may be the only clinical manifestation of a mild abortive attack of any one of a number of diseases, including poliomyelitis, the St. Louis type of encephalitis and epidemic encephalitis. Furthermore, signs of meningeal involvement may be the outstanding feature of other virus diseases, such as herpes zoster and mumps. An incorrect diagnosis in many cases is therefore likely to be made unless an effort is made to determine the etiologic agent in each instance.

POLIOMYELITIS

The possible danger and futility of vaccinating human subjects with recently developed poliomyelitis vaccines, as pointed out in last year's review, were discussed in a recent symposium.[98] Several authorities, especially Rivers and Leake, strongly deprecate the use of vaccines, as proposed by Brodie and by Kolmer. Rivers traces the development of knowledge in regard to vaccination against virus diseases and recalls that killed virus vaccine is ineffective as an antigen and that living virus, while antigenically effective, may produce the disease. Leake [99] recently reported 12 cases in which poliomyelitis developed after vaccination

95. Rake, G.: Some Features of the Epidemiology of Meningococcus Meningitis, Canad. Pub. Health J. **27**:105-110 (March) 1936.

96. Scott, T. F. M., and Rivers, T. M.: Meningitis in Man Caused by a Filterable Virus, J. Exper. Med. **63**:397-414 and 415-432, 1936. Armstrong, C., and Lillie, R. D.: Experimental Lymphocytic Choriomeningitis of Monkeys and Mice Produced by a Virus Encountered in Studies of the 1933 St. Louis Encephalitis Epidemic, Pub. Health Rep. **49**:1019-1027 (Aug. 31) 1934. Armstrong C., and Dickens, P. F.: Benign Lymphocytic Choriomeningitis (Acute Septic Meningitis), ibid. **50**:831-842 (June 21) 1935.

97. Reimann, H. A.: Infectious Diseases, Arch. Int. Med. **56**:382-411 (Aug.) 1935.

98. Symposium on Poliomyelitis, Am. J. Pub. Health **26**:95-112 (Feb.) 1936.

99. Leake, J. P.: Poliomyelitis Following Vaccination Against This Disease, J. A. M. A. **105**:2152 (Dec. 28) 1935.

against the disease. In regard to the same problem Flexner [100] has shown that no evidence is at hand to prove that the treatment of virus with chemicals causes "attenuation." Such treatment either kills the virus or merely reduces or dilutes its concentration; the virulence of that which remains alive is unchanged. When the virus is destroyed it is no longer antigenic; when it is simply diluted it may immunize some animals and cause paralysis in others. [101] Second attacks have been reported to occur among human beings, and monkeys artificially immunized have been successfully reinfected.[102] No evidence exists to show, as claimed by some, that passage of the virus through monkeys removes its power to infect and produce paralysis in man. The use of poliomyelitis vaccine was recently forbidden in California.

Lennette and Hudson [103] cite the work reported since that of Flexner and Lewis in 1910 pertinent to the upper respiratory tract as a portal of entry and of the olfactory nerves as the route by which the virus reaches the central nervous system. They confirm previous observations that transection of the olfactory nerves prevents infection with virus administered intranasally. Similar obstruction to the entrance or passage of virus has been attained by the instillation of various chemicals into the nasal passages before inoculation.[104] Experiments of this type are designed to discover a safe and effective agent to be used as a prophylactic in epidemics of poliomyelitis. Attempts to isolate the virus from the nasopharynges of human beings were not entirely successful.[105] The virus was recovered in only 1 of 26 cases.

Jungeblut [106] has demonstrated "poliocidal" substances of low titer in the tears of normal adult persons. Normal human saliva and spinal

100. Flexner, S.: Concerning Active Immunization in Poliomyelitis, Science **82**:420-421 (Nov. 1) 1935.

101. Olitsky, P., and Cox, H. R.: Experiments on Active Immunization Against Experimental Poliomyelitis, J. Exper. Med. **63**:109-125 (Jan.) 1936.

102. Flexner, S.: Second Attacks and Reinfection in Poliomyelitis, Science **83**:487 (May 22) 1936.

103. Lennette, E. H., and Hudson, N. P.: Relation of Olfactory Tract to Intravenous Route of Infection in Experimental Poliomyelitis, Proc. Soc. Exper. Biol. & Med. **32**:1444-1446 (June) 1935.

104. Armstrong, C., and Harrison, W. T.: Prevention of Experimental Intranasal Infection with Certain Neurotropic Viruses by Means of Chemicals Instilled into Nostrils, Pub. Health Rep. **51**:203-215 (Feb. 21); 241-244 (March 6) 1936. Schultz, E. W., and Gebhardt, L. P.: Prevention of Intranasally Inoculated Poliomyelitis in Monkeys by Previous Intranasal Irrigation with Chemical Agents, Proc. Soc. Exper. Biol. & Med. **34**:133-135 (March) 1936.

105. Paul, J. R.; Trask, J. D., and Webster, L. T.: Isolation of Poliomyelitis Virus from the Naso-Pharynx, J. Exper. Med. **62**:245-257 (Aug.) 1935.

106. Jungeblut, C. W.: Occurrence of Poliocidal Substances in Tears, Saliva and Cerebrospinal Fluid of Normal Individuals, Proc. Soc. Exper. Biol. & Med. **32**:1534-1537 (June) 1935.

fluid were devoid of protective power. Surprisingly, the spinal fluid of monkeys convalescent from poliomyelitis contained no virucidal substances, while such substances were often present in the serum of the same animal.

In another paper Flexner [107] shows that after the nasal instillation of the virus of poliomyelitis monkeys may or may not manifest clinical symptoms but changes invariably develop in the spinal fluid. An increase in the number of cells often occurs within forty-eight hours after inoculation. The cell count is usually higher in animals in which paralysis has developed. Instillations of virus do not lead to active immunity unless clinical symptoms are produced. When no symptoms develop, no antibodies appear in the blood, and the animal is as susceptible to cerebral inoculation as a control monkey. A monkey which has had mild symptoms is immune, and its blood possesses antiviral substances. Essentially similar observations are reported by Jungeblut.[108] If the facts gained by these studies are applied practically, many epidemiologic problems regarding subclinical infection and the evidence of immunity frequently found in normal persons become understandable. As Flexner points out, however, it should be remembered that monkeys probably react differently to the virus than do human beings.

TULAREMIA

The frequency of pulmonary involvement in tularemia is discussed by several observers. Blackford [109] cites the literature on the subject and a description of 7 cases of tularemic pneumonia, 7 cases of tularemia associated with bronchitis and 3 cases of tularemia with pleural effusion which occurred in 35 cases of tularemia. He emphasizes how frequently the thoracic viscera were affected and shows that pulmonary or pleural involvement was detected in 50 per cent of cases of severe disease by clinical examination and in 90 per cent by roentgenographic studies. The presence of pulmonary involvement in cases of atypical manifestations, especially those of the "typhoid" type, is attended with diagnostic difficulties, and a diagnosis of tuberculosis or atypical pneumonia may be made unless the disease is kept in mind or other helpful evidence is obtained from a history of contact infection or by labora-

107. Flexner, S.: The Effects of Nasally Instilled Virus of Poliomyelitis in the Cerebrospinal Fluid and Blood of Monkeys, J. Exper. Med. **62**:787-804 (Dec.) 1935.

108. Jungeblut, C. W.: On the Mechanism of Immunity in Experimental Poliomyelitis, J. Infect. Dis. **58**:150-157 (March-April) 1936.

109. Blackford, S. D.: Pulmonary Manifestations in Human Tularemia, J. A. M. A. **104**:891-895 (March 16) 1935.

tory methods. Roentgenographic studies are described in another paper.[110] Bernstein [111] collected pathologic data from 18 necropsy reports of fatal cases of tularemia. He added 3 of his own cases of tularemia with pneumonia, in which complete necropsy studies were made.

Amoss and Sprunt [112] review reports of several instances of tularemia contracted by the ingestion of undercooked infected rabbit meat and add reports of 2 cases of their own in which the condition was possibly due to the same cause. Here again, in this type of case, the clinical course may be atypical, and the diagnosis may be difficult unless the history is carefully taken and appropriate laboratory tests are made. During the past year I have encountered three examples of unusual sources of infection, one the bite of a playful dog, one a scratch inflicted by a cat and one the bite of a captured field mouse which caused an interdigital ulcer. No other organism is known to inhabit so many different species of animals, birds and insects as Pasteurella tularensis.

Foshay [113] continues to report favorable results obtained in patients treated with specific antiserum. He says that reports of 240 cases in which serum treatment was given and 138 cases in which it was not given show that the duration of the symptoms is shortened by 50 per cent by the serum therapy and that the incidence of suppurative adenitis is lowered but that the duration of fever is not significantly altered. The mortality among the patients who did not receive serum was from 6 to 8 per cent, as compared with 2.5 per cent among those who were treated.

TETANUS

Two more important contributions on tetanus have appeared from Professor Abel's laboratory containing reports of investigations designed to prove that tetanus toxin is distributed by the blood stream and is not transmitted via the nerves to the central nervous sysem. By a number of convincing experiments [114] it is shown that when a minute dose of toxin is injected directly into the sciatic nerve of a dog no symptoms develop if precautions are taken to preclude leakage of the substance into the surrounding tissues. The same small dose, however, when injected into muscle suffices to produce pronounced local rigidity, but when injected intravenously it becomes so diluted and bound to other tissues as

110. Archer, V. W.; Blackford, S. D., and Wissler, J. E.: Pulmonary Manifestations in Human Tularemia, J. A. M. A. **104**:895-898 (March 16) 1935.

111. Bernstein, A.: Tularemia, Arch. Int. Med. **56**:1117-1135 (Dec.) 1935.

112. Amoss, H. L., and Sprunt, D. H.: Tularemia, J. A. M. A. **106**:1078-1080 (March 28) 1936.

113. Foshay, L.: On the Treatment of Tularemia, Ohio State M. J. **31**:21-24 (Jan.) 1935.

114. Abel, J. J.; Hampil, B., and Jonas, A. F.: Researches in Tetanus, Bull. Johns Hopkins Hosp. **56**:317-336 (June) 1935.

to be innocuous. The experiments show that so-called local tetanus is the result of the direct effect of the toxin on the involved muscles and is not due to the influence on the central nervous system. Abel believes that tetanus toxin acts powerfully in a direct manner on all voluntary muscles that have an intact motor nerve terminal, irrespective of the paths by which it reaches them.

The second paper [115] is devoted to historical notes on the pathogenesis of tetanus. The objections to using so "impractical and dangerous" a drug as magnesium sulfate to lessen the convulsions and the disappointing results obtained from the use of other hypnotics are pointed out. Furthermore, since every stage of contracture, inclusive of the terminal one, appears to be due not to an action of toxin on the central motor nuclei but to its direct action on the muscles themselves, the antitetanus serum now available is powerless to prevent the appearance or to retard the process of muscle contractures once the muscles have absorbed the toxin. There is no logic in the use of intraspinal injections of antitoxin either prophylactically or therapeutically.

Doerr [116] has not been able to confirm Abel's results fully. In a number of experiments he showed that the theory of the transportation of toxin exclusively by the blood stream fails to account for certain of the results observed in his experimental animals.

STREPTOCOCCIC INFECTION

Lyons [117] studied the effect of immunotransfusion on infections with hemolytic streptococci. He believes that these organisms produce disease by virtue of their ability to invade the body tissues and by their capacity to form toxins. The septic manifestations are characterized by cellulitis, abscess, inflammation, suppuration, remittent fever, chills and septicemia and the toxic element, by erythema, continuous fever and tachycardia. While I believe that the author overemphasizes the importance of phagocytosis in recovery from infection, one must agree with him that sufficient knowledge is at hand to warrant the therapeutic application of specific antitoxin and antibacterial serum. It is pointed out that because of the diversity of immunologic types of streptococci,[118]

115. Abel, J. J., and Hampil, B.: Researches in Tetanus, Bull. Johns Hopkins Hosp. **67**:343-376 (Dec.) 1935.

116. Doerr, R., and Seidenberg, S.: Dynamische Aktivierung des toxisch induzierten lokalen Tetanus, Ztschr. f. Hyg. u. Infektionskr. **117**:561-569 (Dec.) 1935. Doerr, R.; Seidenberg, S., and Magrassi, F.: Kritische und experimentelle Studien zur Frage des Nachweises von Tetanus Toxin in peripheren Nerven, ibid. **118**:92-116 (March) 1936.

117. Lyons, C.: Immunotransfusion and Antitoxin Therapy in Hemolytic Streptococcus Infections, J. A. M. A. **105**:1972-1975 (Dec. 14) 1935.

118. Swift, H. W.; Lancefield, R. C., and Goodner, K.: The Serologic Classification of Hemolytic Streptococci in Relation to Epidemiologic Problems, Am. J. M. Sc. **190**:445-453 (Oct.) 1935.

commercially prepared polyvalent antistreptococcus serums were found not to possess specific antibodies for his own strains. In his paper methods are described for the selection of a human donor whose blood may contain specific antibodies for the strain of hemolytic streptococcus in question. The patient is then given a transfusion of blood from a suitable donor to combat the sepsis and to neutralize the toxin.

The complexity of the problem of infection and immunity in streptococcic infection is portrayed in studies on erysipelas by Keefer and Spink.[119] They believe that recovery from this infection results from a summation of a number of responses which tend to localize the infection or limit bacterial multiplication. The presence of antibodies which aid in phagocytosis and destruction of the organism seem to be of greatest importance in the process of recovery.

Hamman and Rienhoff[120] reported an interesting case of septicemia due to Streptococcus viridans which was first thought to be subacute bacterial endocarditis. No evidence of cardiac valvular lesions was found, however. The presence of an arteriovenous aneurysm of the external iliac artery and vein, acquired years before, led the authors to suspect that this defect was the focus of infection. That their surmise was correct was shown by the prompt disappearance of septicemia and the recovery of the patient after excision of the defect and by the demonstration of streptococci in the vegetations which partially occluded the opening which had formed between the artery and the aneurysmal sac. This case is an example par excellence of true focal infection. Instances of this type no doubt support the wave of enthusiasm extant regarding the teeth and tonsils, for instance, as foci of infection. Few concepts have so captured the imagination of the medical profession for so long as the theory of focal infection; yet here and there dissenting opinions are expressed. Hamman and Wainwright[121] point out the futility of the indiscriminate extraction of teeth and tonsils for the purpose of influencing general symptoms. Dawson[122] and I[97] have expressed similar views elsewhere.

The streptococcus has recently been incriminated by Rosenow and Butt as the cause of still another disease. Butt[123] studied several cases

119. Keefer, C. S., and Spink, W. W.: Studies of Hemolytic Streptococcus Infection, J. Clin. Investigation **15**:17-19 (Jan.) 1936. Spink, W. W., and Keefer, C. S.: ibid. **15**:21-35 (Jan.) 1936.

120. Hamman, L., and Rienhoff, W. F.: Subacute Streptococcus Viridans Septicemia, Bull. Johns Hopkins Hosp. **57**:219-234 (Oct.) 1935.

121. Hamman, L., and Wainwright, C. W.: Diagnosis of Obscure Fever, Bull. Johns Hopkins Hosp. **58**:109-133 (Feb.) 1936.

122. Dawson, M. H.: Chronic Arthritis, in Nelson Loose-Leaf Living Medicine, New York, Thomas Nelson & Sons, 1935.

123. Butt, H. R.: Myasthenia Gravis: Study of Postmortem Observations Including Demonstration of Gram-Positive Bacteria (Streptococci) in and Between Muscle Fibers, Arch. Path. **21**:27-34 (Jan.) 1935.

of myasthenia gravis and noted collections of lymphocytes and streptococci in stained sections of muscle. It is suggested that these bacteria may be the origin of the toxin that produces the characteristic fatigability in this disease. In experimental studies cultures of streptococci obtained from these patients were shown [124] to produce lesions in the muscles of rabbits resembling the lesions of patients with myasthenia gravis. However, many of the lesions shown in the author's illustrations are characteristic of myositis and not of myasthenia gravis.

The ascribing of the power to cause disease to a few organisms present in diseased muscle is open to serious question. Observations by Reith [125] showed that cocci other than staphylococci existed in muscle tissues in 16 per cent of 108 samples from healthy hogs, rabbits and guinea-pigs. Burn,[126] studying human tissue post mortem, noted that nonhemolytic streptococci were the third most common organism present. The results of Reith and Burn would make it surprising if the ubiquitous nonhemolytic streptococci were not observed occasionally in muscular tissue, especially when diseased, as in myasthenia gravis. Lastly, one is led to speculate on the beneficial effects of the administration of amino-acetic acid which are said to be obtained in myasthenia gravis in relation to the streptococcus as an etiologic agent.

STAPHYLOCOCCIC INFECTION

A number of important contributions concerning staphylococci have appeared during the year. An outbreak of food poisoning due to staphylococci involving 206 persons was reported.[127] All the patients recovered within a few hours. Blackman [128] discusses an example of staphylococcic infection of the small intestine associated with septicemia. Death occurred within thirty-six hours. At autopsy, acute inflammation and many staphylococci were noted in the walls of the jejunum and part of the ileum. Rigdon [129] reports 7 cases of staphylococcic infection with evidence of renal damage. He believes that the thrombi present in the capillary loops may be the result of the necrosis and

124. Rosenow, E. C., and Heilman, F. R.: Bacteriologic Studies in Myasthenia Gravis, Proc. Soc. Exper. Biol. & Med. **34**:419-425 (May) 1936. Boothby, W.: Myasthenia Gravis: A Discussion of Its Etiology, read before the Association of American Physicians on May 5, 1936.

125. Reith, A. F.: Bacteria in the Muscular Tissues and Blood of Apparently Normal Animals, J. Infect. Dis. **12**:367-383, 1926.

126. Burn, C. G.: Postmortem Bacteriology, J. Infect. Dis. **54**:395-403, 1934.

127. Dack, G. M.; Bowman, G. W., and Harger, R. N.: An Outbreak of Food Poisoning Apparently Due to Staphylococci, J. A. M. A. **105**:1598 (Nov. 16) 1935.

128. Blackman, S. S.: Acute Staphylococcal Infection of the Jejunum and Ileum, Bull. Johns Hopkins Hosp. **57**:589-594 (Nov.) 1935.

129. Rigdon, R. H.: Renal Lesions in Staphylococcus Aureus Infections and Their Relation to Acute Glomerular Nephritis, Arch. Int. Med. **57**:117-131 (Jan.) 1936.

fusion of endothelial cells. The presence of erythrocytes in the glomerular spaces and of albumin, red cells and casts in the urine is the result of a toxin liberated by the staphylococci. The damage to the kidney is usually insufficient to produce clinical evidence of glomerulonephritis.

Important work on the classification of staphylococci is reported by Julianelle and Wieghard.[130] They find the agglutination test less reliable for this purpose than the precipitin test made with purified carbohydrate derivatives of staphylococci. With the latter test the organisms fell into two distinct types, those from infected human beings falling into type A and those from other sources into type B. Studies of this kind are necessary before the specific therapy of staphylococcic infections can be satisfactorily developed.

MacNeal and Frisbee[131] report the results of the use of bacteriophage in the treatment of 100 patients with staphylococcic bacteremia. Although 75 of these patients died, the authors state that the staphylococcic infection of the blood stream was definitely influenced and that bacteriophage is at times live-saving. Before one accepts the therapeutic value of bacteriophage for this type of infection, several points must be considered. In the first place, in order to evaluate its effectiveness, the results in patients with similar manifestions who have and those who have not received bacteriophage must be compared. To include cases in which there were serious primary conditions, like carbuncles, with those of simple bacteremia, obviously distorts the statistical analysis. For example, transitory bacteremia with staphylococci and other organisms was found in 16 of 51 patients after tonsillectomy by Fischer and Gottdenker,[132] who concluded that bacteremia of this type is not rare and seldom leads to serious consequence. Of MacNeal's 25 patients who received treatment and who recovered, there were many who apparently suffered from a mild infection, as far as can be gathered from the data given, and only 5 of these were over the age of 30. In Scott's[133] study of septicemia, the mortality rate among patients with staphylococcic sepsis not treated with bacteriophage was similar, 79 per cent. From an academic point of view, Evans has shown that bacteriophage is inactivated by blood, pus, ascitic fluid and saliva. No evidence exists of the lytic action of bacteriophage in vivo. Furthermore, the concentration after injection into the blood stream is far too weak to produce a lytic action, and finally there is as yet no unanimity

130. Julianelle, L. A., and Wieghard, C. W.: The Immunological Specificity of Staphylococci, J. Exper. Med. **62**:11-21 (July) 1935.

131. MacNeal, W. J., and Frisbee, F. C.: One Hundred Patients with Staphylococcus Septicemia Receiving Bacteriophage Service, Am. J. M. Sc. **191**:179-195 (Feb.) 1936.

132. Fischer, J., and Gottdenker, F.: Transitory Influx of Bacteria into the Blood Stream After Tonsillectomy, Wien. klin. Wchnschr. **49**:177 (Feb. 7) 1936.

133. Scott, W. J. M.: The Principles of the Treatment of Septicemia, J. A. M. A. **105**:1246-1249 (Oct. 19) 1935.

of opinion as to what bacteriophage really is. Until it is shown that recovery, when it does occur, is the result of the specific action of bacteriophage on the staphylococcus and is not due to the nonspecific shock which usually follows such treatment, the procedure must be regarded as purely experimental. Scott concludes that the most important principle in the treatment of septicemia in general is the eradication or exclusion from the circulation of foci that cause reinfection of the blood. No chemotherapeutic agent has been found to be of value. Transfusion is a supportive measure. The most hopeful line of progress, he believes, is the development of an immune serum specific for the infecting organism, which can be given early in the course of the septicemia.

RICKETTSIAL DISEASES

Parker [134] has published his results of ten years' experience in prophylaxis against Rocky Mountain spotted fever with vaccine. It was found that vaccine prepared by treating virus-laden adult wood ticks with a phenol-formaldehyde mixture evoked a significant degree of protection against the disease. The degree of immunity produced was usually sufficient to afford full protection against relatively mild strains and appeared to ameliorate the symptoms produced by virulent strains sufficiently to insure the recovery of the infected persons. Annual vaccination is recommended for those living in areas where the virulence of Rickettsia is known to be high. The dosage prescribed is two subcutaneous injections of 1 cc. each for children under 10 and two or three injections of 2 cc. each for adults.

Two investigators from Morocco [135] report the successful vaccination of natives against typhus by inoculating them with living virus treated with bile. Although the use of living virus as a vaccine is deprecated as a dangerous practice, no bad effects were mentioned. Other investigators [136] have protected guinea-pigs against the European louse-borne typhus with the serum of a horse immunized with killed Rickettsia of the Mexican flea-borne murine type, thus providing further evidence of the close relationship of the two forms. Further reports [137] of a similar relationship of typhus viruses in another part

134. Parker, R. R.: Rocky Mountain Spotted Fever: Results of Ten Years' Prophylactic Vaccination, J. Infect. Dis. **57**:78-93 (July-Aug.) 1935.

135. Vaccination Against Typhus with a Living Virus, foreign letter, J. A. M. A. **105**:524 (Aug. 17) 1935.

136. Zinsser, H.; Castaneda, M. R., and Hager, F. D.: Protective Action of Concentrated Antityphus Serum (Murine Type) Against European Typhus Virus, Proc. Soc. Exper. Biol. & Med. **33**:44-47 (Oct.) 1935.

137. (*a*) Lewthwaite, R., and Savoor, S. R.: The Typhus Group of Diseases in Malaya, Brit. J. Exper. Path. **17**:1-34 (Feb.) 1936. (*b*) Kligler, I. J.; Aschner, M., and Levine, S.: Comparative Studies of the Louse-Borne (Epidemic) and Flea-Borne (Murine) Typhus Viruses, ibid. **17**:53-60 (Feb.) 1936. (*c*) Pijper, A., and Dau, H.: South African Typhus, J. Hyg. **35**:116-124 (Feb.) 1935.

of the world have appeared. Lewthwaite and Savoor [137a] have shown a relationship between so-called rural and urban (flea-borne) tropical typhus in Malaya. Pijper [137c] has shown that three forms of typhus-like diseases occur in South Africa: tick-bite fever, flea typhus and louse typhus.

These studies show that typhus is widely distributed throughout the world. The variety found in any given place may be modified by passage through different insect or animal hosts. Somewhat similar variations in Rocky Mountain spotted fever have been noted in this country. The so-called eastern and western strains vary in the clinical manifestations they produce and in their behavior in guinea-pigs. There is evidence that a third and even milder form exists in the midwestern states.[138] The widespread nature of the disease raises the question of abandoning the restrictive term Rocky Mountain. It would be better, perhaps, if this group of diseases were simply named tick fever or spotted fever. The latter term is less preferable, since it has long been applied to other infections.

Several studies on the Weil-Felix reaction have been carried on in Zinsser's laboratory. In one [139] it was found that about 15 per cent of serums from persons not suffering from infections gave the Weil-Felix reaction in a titer of 1:40 or 1:80. In a few instances the titer was as high as 1:160. Another study [140] apparently solved the riddle of the curious serologic relationship between Rickettsia Prowazeki and Bacillus proteus X 19, which is the basis of the Weil-Felix reaction. Castaneda found that one of the two polysaccharides derived from B. proteus X 19 is immunologically similar to the antigenic factor in R. Prowazeki.

A modern classification of human rickettsial disease is conveniently illustrated in the accompanying table prepared by Felix.[141]

MALARIA

In October 1934 an epidemic of malaria began in Ceylon which subsequently exceeded all previous ones in magnitude.[142] It reached its height in December 1934, abated somewhat until April 1935, when

138. Reimann, H. A.: Rocky Mountain Spotted Fever in Minnesota, Minnesota Med. **19**:343-346 (June) 1936.

139. Savoor, S. R.; Castaneda, M. R., and Zinsser, H.: Notes on the Weil-Felix Reaction in Individuals Not Suffering from Typhus, Proc. Soc. Exper. Biol. & Med. **33**:365-366 (Dec.) 1935.

140. Castaneda, M. R.: The Antigenic Relationship Between B. Proteus X19 and Rickettsia, J.Exper.Med. **62**:289-296 (Sept.) 1935.

141. Felix, A.: The Serology of the Typhus Group of Diseases, Tr. Roy. Soc. Trop. Med. & Hyg. **29**:113-118 (July) 1935.

142. The Ceylon Malaria Epidemic 1934-1935: Report by the Director of Medical and Sanitary Service, Colombo, 1935, p. 1.

another wave overwhelmed the whole area, and finally subsided in June. Of 3,100,000 persons in the so-called wet zone, approximately 1,500,000 were infected. There were 90,000 deaths, which was more than double the usual number of deaths from malaria in this section of the island. In other regions the death rate from malaria was about one-third more than usual. This unprecedented outbreak was attributed to abnormal weather conditions. In the wet zone the region is densely populated, the rivers are almost always full and the conditions are usually unfavorable for the breeding of Anopheles mosquitoes. In the so-called dry zone malaria is endemic. The season after April 1934 was unusually dry, so that many of the flowing streams became a series of puddles, which were somewhat replenished by light rainfalls in July and October,

Typhus Group of Fevers (After Felix)

	Subgroup		
	Type × 19	Type ×K	Type Undetermined
Name of disease..	Classic epidemic typhus Tabardillo Endemic typhus (Brill's) of United States, Australia, Greece, Syria, Manchuria, Malaya (shop typhus) and Toulon (fièvre nautique)	Japanese river fever (Tsutsugamushi fever of Japan, Malaya and Netherlands Indies) Malay scrub typhus Scrub typhus of East Indies	Spotted fever of Rocky Mountains Sao Paulo endemic typhus Fièvre boutonneuse Febbre errutiva Tick bite fever of South Africa Epidemic and endemic typhus of South Africa
Vector.....	Lice and rat fleas	Mites	Ticks, lice and rat fleas
Reservoir of virus	Rats Man	Field mice and rats	Rodents Dogs Ticks ? Man
Agglutination....	× 19 +++ × 2 + ×K —	× 19 — × 2 — ×K +++	× 19 + × 2 + ×K +

thus furnishing suitable pools for mosquito breeding. In Ceylon eighteen varieties of Anopheles are found, which breed only in the dry zone. The rarely encountered variety Anopheles culicifacies is found only in the wet zone. Conditions in the wet zone in 1934 were therefore ideal for the multiplication of A. culicifacies, which subsequently appeared in unprecedented numbers and apparently was responsible for the epidemic. The epidemic began in a small village and spread rapidly down stream and finally over the island. In certain isolated localities the death rate was eight times higher than usual. In children less than 5 years old the condition was especially fatal. Many deaths were due to complications. In cases in which there were symptoms of cerebral involvement, chiefly due to Plasmodium falciparum infection, the condition was often fatal. Dysentery and pneumonia occurred frequently. Plasmodium vivax was found in 62 per cent of cases, P. falciparum in 36 per cent and Plasmodium malariae in 1 per cent.

Quinine therapy was successful in general, but relapses frequently occurred. Quinine sulfate and quinine bisulfate were most commonly used. Plasmochin and atabrine were used only when conditions provided the opportunity for constant observation, because of the liability of untoward side-effects. When atabrine was used, two injections usually sufficed, but similar results were obtained also with two intramuscular injections of quinine hydrochloride. The impression was gained that relapses after the use of atabrine by mouth were less frequent than after long continued treatment with quinine and that both procedures were better than two parenteral injections of atabrine.

The details of this epidemic are related to illustrate what a profound influence meteorologic conditions may have on the development and spread of epidemic disease. In the case cited two of the three factors required for the outbreak of an epidemic were at hand, the reservoir of infection in chronic carriers and the susceptible hosts. The means for transmission of the micro-organism from the carriers to the hosts were lacking until weather conditions favored the breeding of mosquitoes. The outbreak calls to mind forcibly the dangers constantly confronting populations when the usual biologic equilibrium is upset by war, flood, drought or other catastrophes.

Blackwater Fever.—Although blackwater fever is now generally recognized as being invariably associated with malaria, if not actually being malaria, Fernán-Núñez [143] claims that it is practically the one remaining tropical disease the etiology of which has not been definitely determined. He suggests that the disease is an allergic manifestation of malaria which quinine aids in precipitating. Previous views have held that in blackwater fever the red blood cells of a patient treated with large doses of quinine salts are unusually susceptible to intravascular lysis or that quinine salts act as lysins for red blood cells that are already weakened by the intravascular lysins incident to the disease. The recent work of Ponder and Abels [144] shows that quinine hydrochloride is a simple hemolysin in vitro. They believe it unlikely that quinine salts produce intravascular lysis, since the low concentration attained would not cause lysis even in a solution of sodium chloride. Quinine salts do, however, bring about a decreased resistance of the red blood cells and accelerate other intravascular lysins.

MISCELLANEOUS INFECTIONS

Measles.—According to McKhann and Chu, immune globulin obtained from the human placenta is effective as a prophylactic agent against

143. Fernán-Núñez, M.: Blackwater Fever, Ann. Int. Med. **9**:1203-1212 (March) 1936.

144. Ponder, E., and Abels, J. C.: Effect of Quinine Hydrochloride on Resistance of Rabbit Red Cells, Proc. Soc. Exper. Biol. & Med. **34**:162-165 (March) 1936.

measles. The product is now commercially available, and its merits have been considered by the Council on Pharmacy and Chemistry of the American Medical Association,[145] which has decided to postpone recognition of the product until more evidence of its value is at hand. Other studies [146] suggest the curative value of the substance. An injection of 2 cc. caused modification of the infection in 13 of 18 cases.

Rabies.—In the city of New York in 1934 over 19,000 persons were bitten by dogs, and 44 per cent of the dogs tested were found to be rabid.[147] It is surprising and disappointing to learn that there has been a steady increase in dog bites in New York and that the death rate from rabies, in spite of the use of prophylactic vaccine, has not been lowered in twenty-five years. The Pasteur prophylactic method does not invariably protect the patient, as commonly believed. Sixty fatal cases of rabies were reported in the United States in 1933. The best method of control of the disease lies in the muzzling, leashing or elimination of biting dogs and in placing the responsibility and liability on the owners of dogs. Vaccination of dogs against rabies is still in the experimental stage.

Dengue.—Cheney [148] reports 6 cases of an unusual syndrome characterized by severe aching pains and a high, usually biphasic, fever lasting about a week, without symptoms of involvement of the respiratory tract or of leukocytosis. He suggests that the disease is a new entity in California and closely resembles dengue. The disease was reproduced in 4 other persons by inoculation of blood from a patient. He suggests that pleurodynia may be a form of dengue. According to the surgeon general's report for 1935, 2,000 cases of dengue occurred in Florida in 1934, 1,962 in Georgia and 1,072 in Alabama. The actual number of cases is undoubtedly much larger, since many cases are not reported. Incidentally, in the same report mention is made of 5,371 cases of smallpox in 1934, the smallest number reported since records have been kept.

Plague.—A rather alarming outbreak of plague among squirrels in California was recently reported by Kellogg.[149] Many of the animals found dead showed evidence of pulmonary involvement, while others

145. Preliminary Report of the Council on Pharmacy and Chemistry, J. A. M. A. **105**:510-512 (Aug. 17) 1935.

146. Levitas, I. M.: Treatment, Modification and Prevention of Measles by Use of Immune Globulin (Human), J. A. M. A. **105**:493-496 (Aug. 17) 1935.

147. Oleson, R.: Control of Rabies in New York City, Pub. Health Rep. **50**: 1087-1106 (Aug. 16) 1935.

148. Cheney, G.: Appearance of a Dengue-Like Fever in Northern California, Arch. Int. Med. **56**:1067-1096 (Dec.) 1935.

149. Kellogg, W. H.: Rodent Plague in California, J. A. M. A. **105**:856-859 (Sept. 14) 1935.

apparently died from septicemia too soon for pulmonary lesions or other evidence of focal necrosis to develop. Kellogg points out the potential danger of the outbreak, its widespread nature and the permanence of the plague problem on the Pacific coast. According to the surgeon general's report, fatal cases of plague occurred in Oregon in May, and in Tulare County, Calif., in June 1934. Plague-infected rodents were found in Oregon and in Montana.

A French investigator [150] reports success in vaccinating natives of Madagascar with living plague organisms. While this procedure appears to be highly dangerous, he claims that no accidents occurred among 47,000 vaccinated natives. The procedure was said to have reduced the death rate from plague materially.

L. T. Wu [151] has recently published a detailed history of two Manchurian outbreaks of plague.

Anthrax.—Gold [152] reported 10 cases of anthrax which developed in persons working with goat hair imported from China and India. Antianthrax serum seemed to be of benefit in causing the temperature and pulse rate to return to normal but without effect on the adenopathy. In some cases bacilli were recovered from the lesion after the patient had apparently recovered.

Typhoid.—The first important advance in the experimental attack on typhoid in years was announced by Rake.[153] He succeeded in enhancing the pathogenicity of typhoid bacilli for mice by inoculating them with mucin, which sometimes increased the virulence a million times. By this means he was enabled to test the efficiency of immune serum from vaccinated persons in protecting mice from infection. It was found that the Widal reaction of the serum did not run parallel with the protective power. It was never positive except in serum containing protecting antibodies. Two serums which afforded protection, however, did not contain agglutinins for the antigens used. Rake believes that the protective test is more delicate for detecting serologic changes than the Widal reaction.

Crystalline Virus.—Highly important studies on the nature of diseases of plants (tobacco-mosaic disease) due to a filtrable virus were

150. Vaccination Against Plague with a Living Virus, foreign letter, J. A. M. A. **105**:1283 (Oct. 19) 1935.

151. Wu, L. T.: Manchurian Plague Prevention Service; Memorial Volume, 1912-1932, Shanghai, China, National Quarantine Service, 1934.

152. Gold, H.: Studies in Anthrax: Clinical Report of Ten Human Cases, J. Lab. & Clin. Med. **21**:134 (Nov.) 1935.

153. Rake, G.: Enhancement of Pathogenicity of Human Typhoid Organisms by Mucin, Proc. Soc. Exper. Biol. & Med. **32**:1523-1524 (June) 1935.

made by Stanley.[154] He succeeded in obtaining a crystalline protein from infected tobacco and tomato plants by fractionation of the globulin in the plant extract, which had the properties of the virus. The substance formed fine needle crystals; it was precipitated by protein precipitants, and it reproduced typical mosaic disease when introduced into fresh plants. Repeated recrystallization left the infective properties unchanged. When the virus was injected into animals serum precipitins for solutions of crystals developed in dilutions up to 1:100,000. Animals immunized with crystals showed precipitins for the crystalline protein and for the juice of infected plants but not for the juice of normal plants.

If it can be proved beyond doubt that none of the actual virus was carried over in the processes of recrystallization, this work is of great significance, and it supports earlier suggestions regarding the possibility that nonliving substances can multiply on living tissues to produce disease.

BACTERIAL INVASION

Although many theories have been propounded to account for the invasion of the body by pathogenic bacteria, the subject is still obscure. Experimenters during the past half century have devoted most of their attention to the life history and habits of various bacteria, and it is only within the past decade or so that the attention of numerous investigators has been concentrated on the actual conflict of bacteria with their hosts. Attempts have been made to determine why some bacteria are at times invasive, how and where they invade, what changes occur in the host as a result of invasion and whether the so-called defensive mechanism of the host is a purposeful reaction developed against age old exposure to a given organism or whether man, for example, has survived because his tissues "happen" to react in a manner which renders the growth or existence of bacteria impossible.

Among investigators actively interested in this field in recent years may be mentioned Gay, Shwartzman, Cannon, Rich, Goodner, Menkin, Duran-Reynolds, Robertson and many others. Limitation of space prevents discussion of all but a few papers, even of those published during the past year.

Much of the recent work has already been discussed by Menkin.[155a] This author showed experimentally that virulent pneumococci when

154. Stanley, W. M.: Isolation of a Crystalline Protein Possessing the Properties of Tobacco-Mosaic Virus, Science **81**:644-645 (June 25) 1935; The Isolation of Crystalline Tobacco-Mosaic Virus Protein from Diseased Tomato Plants, ibid. **83**:85 (June 24) 1936.

155. Menkin, V.: (*a*) Inflammation and Bacterial Invasiveness, Am. J. M. Sc. **190**:583-596 (Nov.) 1935; (*b*) Studies on Inflammation, J. Infect. Dis. **58**:81-91 (Jan.-Feb.) 1936; (*c*) A Summary of the Effect of Ferric Chloride in Tuberculous Rabbits, Proc. Soc. Exper. Biol. & Med. **34**:262-266 (March) 1936.

injected into normal skin rapidly diffuse and cause death from septicemia. If, however, the area into which bacteria were injected was first treated with some substance which caused local inflammation, the bacteria were then hemmed in by a mechanical barrier of thrombosed lymphatic vessels and coagulated plasma. The localization of bacteria in situ resulted in a prolongation of the survival of the host. In other experiments [155b] Menkin produced a local area of inflammation in the skin and subsequently injected certain substances intravenously. The injected substances accumulated at the established focus in the skin, which he believes was the result of increased permeability of the capillaries at the site of inflammation. This may be an important point in connection with localization of infection, since antibodies which are closely associated with globulins may thus diffuse through the injured capillaries and accumulate at the site of entry of bacteria. The author believes that the reaction noted explains in part, at least, the Shwartzman phenomenon (when a filtrate of certain pathogenic organisms is injected into an area of the skin of rabbits, the area becomes the site of an intense local reaction if twenty-four hours later more of the same filtrate is injected intravenously). Menkin believes the Shwartzman reaction is nonspecific and dependent on the principles just mentioned. The same author [155c] also demonstrated an accumulation of ferric chloride in tuberculous areas in rabbits after intravenous injections and a definite retardation of the disease. The study has been extended to clinical cases.

Menkin's experiments recall the conclusions of Krause, published in 1926, which showed that the inflammatory allergic reaction at the site of inoculation of tubercle bacilli caused a "fixation" of bacteria at the site of injection and delayed or prevented further invasion. In spite of much experimental evidence to the contrary, it has seemed to me that the views of Krause are largely correct. While it appears true that severe allergic response is harmful, its dangers seem to have been exaggerated. A certain degree of allergy may provide conditions favorable for the restriction of bacteria at the site of entry.

Another interesting study in regard to localization of bacteria was made by Nedzel,[156] who injected pitressin to produce transient spasm and anoxemia in tissues of the central nervous system. He then injected bacteria intravenously and demonstrated their presence in the area involved in the pressor effects. The capillaries of these regions, it was assumed, became more permeable, sticky and dilated, thus retarding the blood flow and permitting the adhesion of the bacteria to the walls of the capillaries.

---

156. Nedzel, A. J.: Pressor Reactions and Bacterial Localization in the Central Nervous System, Proc. Soc. Exper. Biol. & Med. **34**:239-240 (March) 1936.

Many experimenters in this field have employed pneumococci. Teale [157] claims that the initial clearance of pneumococci from the circulation in immune animals was accomplished solely by phagocytic cells and not by circulating antibodies, since none could be demonstrated. The chief factor in immunity, he believes, is the state of the tissues with regard to the infecting bacteria. Goodner and Miller [158] state that antipneumococcus serum owes its protective properties to (1) the specific neutralization of the capsular substance of the pneumococci, (2) agglutination of the bacteria to permit phagocytosis and (3) the sensitization of the organism, which favors intracellular digestion. Robertson [159] presents evidence to show the importance of macrophages in recovery from pneumonia. In histologic studies of lungs, lesions exhibiting a well developed macrophage system were regularly characterized by a relative infrequency of pneumococci as compared with other involved areas.

Other investigators place more emphasis on humoral immunity in contrast with cellular immunity, thus perpetuating the controversy which originated with Metchnikoff. It is probable that most of the views discussed here are essentially correct. The matter is infinitely complex; "the number of forces or factors involved in the production of the end result is very large. Infection represents a constant state of flux and the tendency in either direction toward a state of equilibrium is constantly influenced by numerous opposing forces, often confusingly interrelated." [158]

The views of Rich and McKee [160] do not support those of Teale. These investigators have shown that immunized rabbits rendered leukopenic by benzene are capable of localizing pneumococci at the site of infection in the absence of leukocytes, in contrast with normal unimmunized animals. The authors believe that the presence of humoral immune antibodies causes prompt clumping and localization before an inflammatory exudate has a chance to accumulate. This point is also used to minimize Krause's views regarding the importance of allergic reaction, since Rich believes the retardation of bacterial spread occurred before the tissue response could develop. Humoral antibodies therefore appear to prevent the immediate spread of bacteria by holding them

157. Teale, F. H.: Some Observations on the Relative Importance of the Reticulo-Endothelial Tissues and the Circulating Antibody in Immunity, J.Immunol. **28**:133-160, 1935.

158. Goodner, K., and Miller, D. K.: The Protective Action of Type I Antipneumococcus Serum in Mice, J.Exper.Med. **62**:375-391 (Sept.) 1935.

159. Robertson, O. H., and Uhley, C. G.: Changes Occurring in the Macrophage System of the Lungs in Pneumococcus Lobar Pneumonia, J. Clin. Investigation **15**:115-130 (Jan.) 1936.

160. Rich, A. R., and McKee, C. M.: A Study of the Character and Degree of Protection Afforded by the Immune State Independently of the Leucocytes, Bull. Johns Hopkins Hosp. **54**:277-314 (April) 1934.

fixed at the site where they lodge until phagocytic leukocytes gather and destroy them. Robben's [161] results do not show that phagocytic activity, as observed in free cells of the peritoneal cavity, is a factor in successful resistance against experimental pneumococcic infection. No differences in cellular response were noted in animals experimentally inoculated, whether death or recovery ensued. Dixon and McCutcheon,[162] studying chemotropism, recently presented evidence to show that human polymorphonuclear leukocytes when reacting to attraction by bacteria in vitro travel at no greater rate than when moving at random. Drinker and his associates [163] studied the effect of immune serum on pneumococci in the thoracic lymph. According to their experiments pneumococci invaded the lymph and multiplied rapidly. Immune serum may remove them from the blood, but it cannot attain sufficient concentration in the lymph to be effective. The lymphatic glands, therefore, may serve as a source of reinfection unless the antibody content of the blood is constantly replenished. The authors believe that additional factors, probably cellular in nature, also play a rôle in recovery.

Several years ago I demonstrated the effect of a slight increase of viscosity on the enhancement of specific agglutination of pneumococci. Solutions of acacia adjusted to a viscosity of about 5.6 caused marked clumping of pneumococci in vivo in the presence of antipneumococcus serum in amounts too small to be effective unassisted. The experiments were planned to determine whether or not the increase in globulins and viscosity of the blood so commonly noted in infection has any significance in the process of recovery. These observations have been confirmed and extended by Catron.[164] Pneumococci suspended in solution of acacia and injected into animals caused death sooner than organisms suspended in saline solution, but in the presence of a small amount of immune serum the pneumococci were localized and destroyed. The experiments are of interest when compared with those of Miller and of Rake, who show that meningococci or typhoid bacilli are much more invasive in a mucinous suspension than when suspended in broth. It appears that a certain range of viscosity may act as a deterrent to bacterial spread, espe-

161. Robben, F. J.; Rich, G. T., and Fleisher, M. S.: Studies on Spontaneous Recovery from Pneumococcic Infection in the Guinea-Pig, Arch. Path. **20**:46-63 (July) 1935.

162. Dixon, H. M., and McCutcheon, M.: Chemotropism of Leucocytes in Relation to the Rate of Locomotion, Proc. Soc. Exper. Biol. & Med. **34**:173-176 (March) 1936.

163. Drinker, C. K.; Enders, J. F.; Shaffer, M. F., and Leigh, O. C.: The Immigration of Pneumococci Type III from the Blood into the Thoracic Duct Lymph of Rabbits, and the Survival of These Organisms in the Lymph Following Intravenous Injection of Specific Antiserum, J.Exper.Med. **62**:849-860 (Dec.) 1935.

164. Catron, L.: Studies in Bacterial Localization, J. Exper. Med. **61**:735-752 (June) 1935.

cially in the presence of immune serum, but a markedly viscous menstruum seems to protect bacteria from antibodies or phagocytes and to provide conditions favorable for growth. Du Noüy [165] demonstrated a momentary increase in viscosity when the specific antigen was added to immune serum. The reaction was specific. Pesch and Damm [166] have demonstrated pneumococcidal properties of human saliva which are most effective at body temperature and are weakened after heating to 56 C. or after filtration. Pneumococci cultivated in saliva rapidly lost their virulence for mice, and occasional dissociation into avirulent forms occurred.

All the work on bacterial invasiveness and host response still leaves many facts unexplained, among them the observation that type-specific, unchanged virulent pneumococci may be recovered from the lung after the crisis of pneumonia when the patient is well and from the lesions of rabbits which survive experimental dermal infection (Goodner). Numerous other examples of the presence and survival of organisms at the site of infection after recovery of the host exist.

In a recent address Meyer [68] discussed the important question of latent and symptomless infections. The term "latent infection," he believes, should denote merely the presence of a pathogenic organism in or on the body against which there has been no reaction. A representative example may be the existence of typhoid bacilli in the intestinal tract of a healthy carrier who has never had typhoid. The condition of latency, he believes, is conditioned chiefly by the behavior of the host, although localization of the organism or other behavior of the pathogen may influence the course. The terms "symptomless" or "inapparent infection" should apply to that state when pathogens actually invade the blood or tissues after a certain incubation period, evoke immune reactions and finally disappear without the manifestation of clinical or anatomic symptoms or signs of illness in the host; in other words, the virus is distributed in the usual time, location and quantity as found in a given clinical infection, except that no clinical evidence of disease develops. It seems that a third grouping should be made to accommodate the so-called abortive infections, such as the mildest forms of scarlet fever without the rash, of poliomyelitis without paralysis and of typhus without the eruption. The various gradations of clinical manifestations of any given disease seem to be due not to fluctuations of virulence of the infecting organism but rather to differences in the resistance of the host, which may be dependent on genetic factors.

165. Du Noüy, L.: Immunological Reactions and Viscosity, Science **82**:254 (Sept. 13) 1935.

166. Pesch, K. L., and Damm, R.: Ueber die bactericide und virulenzvermindernde Wirkung von Speichel auf Pneumokokken, Ztschr. f. Hyg. u. Infektionskr. **118**:1-16 (March) 1936.

Meyer believes that in the question of latent, symptomless or subclinical infection lies the key to the understanding of latent epidemization and of the rise and fall of certain epidemic diseases. One wonders whether or not the existence of latent or symptomless infections will perennially frustrate any completely successful attempts to control infectious disease.

Gowen [167] recently published a brief review of studies on genetic constitution as a factor in disease and showed how the development of pathologic changes is often an expression of the host's inheritance rather than of the variability of the pathogens. The segregation of specific genes for susceptibility and resistance to disease initiated by pathogens may be responsible for immunity, morbidity or mortality within an exposed population.

167. Gowen, J. W.: Genetic Constitution as a Factor in Disease, Sigma Xi Quart. **23**:103-117 (Sept.) 1935.

Book Reviews

Diseases of the Thyroid Gland. By Arthur E. Hertzler, M.D., Chief Surgeon, Halstead Hospital; Professor of Surgery, University of Kansas. With a chapter on **Hospital Management of Goiter Patients,** by Victor E. Chesky, M.D., Chief Resident Surgeon, Halstead Hospital. Third edition. Price, $7.50. Pp. 348, with 181 illustrations. St. Louis: C. V. Mosby Company, 1935.

To the internist it appears that thyroid disease has been regarded from a wholly surgical point of view. One gets the impression that thyroid enlargement is a condition in which surgical intervention is always indicated and that medical management is to be considered only as a preoperative measure or, perhaps, until the surgeon decides on a convenient time to operate.

Today such an attitude seems a bit irrational. Surely some patients with thyroid enlargement live out their life expectancy with the thyroid undisturbed, and doubtless some die from causes other than thyroid disease. It seems possible that some goiters may regress and disappear without untoward symptoms. Frank thyrotoxicosis has been known to undergo spontaneous and permanent remission. Such instances appear to be unknown to this author.

The etiology of thyroid disease is still obscure, and this obscurity is not lessened by Hertzler's discussion. He hesitates to state that deficiency of iodine produces simple goiter elsewhere than in Dayton, Ohio. In the interest of accuracy, it should be pointed out that the work of Marine and Kimball was done at Akron, Ohio, and has been confirmed in many other localities.

The discussion of the symptomatology of the hyperthyroid state is shrouded in much the same obscurity. Apart from the well recognized symptoms of thyrotoxicosis, Hertzler sets out a group of symptoms so intangible and ambiguous that they would warrant a diagnosis of hyperthyroidism in almost any case of nervous instability. This is particularly true in view of the fact that he considers an elevation of the metabolic rate unnecessary for diagnosis.

In the author's opinion the treatment is entirely surgical. His aversion to compound solution of iodine, U. S. P., except as an immediate preoperative measure, and his fear of the results of the long continued use of iodine seem unwarranted in the light of more recent investigation.

When one approaches the subject of the surgical removal of the thyroid the picture is different. Here Hertzler shows complete familiarity with a highly technical subject. All varieties of surgical approach, the removal of abnormally placed glands, the manner of dealing with complications and the preoperative and postoperative care in the hospital are adequately dealt with.

The book is well and profusely illustrated but contains no bibliography.

Classical Contributions to Obstetrics and Gynecology. By Herbert Thoms. Price, $4. Pp. 265, with 57 illustrations. Springfield, Ill.: Charles C. Thomas, Publisher, 1935.

Few publishers have had the satisfaction of offering volumes of medical classics which approach in quality and enjoyment those which bear the mark of Charles C. Thomas, Publisher. The reception accorded "Classical Descriptions of Diseases," "Selected Readings in Pathology," and others undoubtedly influenced the publishers to add to the series.

This book marks another venture into obstetric history for Herbert Thoms. It is larger and more comprehensive than his chapters in "American Obstetrics" and is modeled to the pattern established by Major's "Classical Descriptions of

Diseases." It contains the more notable contributions to the two sciences of obstetrics and gynecology, in the original wording of their creators, with short biographic sketches of the contributors.

The chapters are arranged so as to group the material into general subjects, and in these various groupings the essays are presented in chronological order. As an example, the chapter on puerperal fever contains the writings of Hippocrates, Alexander Gordon, Charles White, Holmes, Semmelweis and Pasteur on this subject. As the reader progresses he leaves Gordon, who first demonstrated the infectiousness of the condition, to find Holmes, who showed its contagiousness; with Semmelweis he traces the modes of transmission and finally reads the words of Pasteur describing the experiments which proved beyond question the source and nature of the disease and the organisms most commonly responsible for it.

The names of a few physicians, such as Smellie, Harvey and Mauriceau, appear in more than one chapter, in accordance with the greatness of these men. The biographic sketches are fairly complete, if their brevity is considered, and are amply sufficient for their purpose.

The contributions to gynecology are all contained in one short chapter. This subject has been slighted for its older associate, obstetrics. Papers by McDowell, Nathan Smith, Atlee, Sims, Tait, Wells and Noeggerath are included.

No living authors are represented, and no material written since 1900 is used. This, in part, may explain the shortness of the chapter devoted to gynecology. Future generations will, no doubt, add many names, well known in the past thirty-five years, to the author's list.

The Treatment of Acute Poisoning. By H. L. Marriott, M.D., Resident Medical Officer, The Middlesex Hospital, London. Price, 5 shillings. Pp. 57, with 15 illustrations. London: John Murray, 1935.

This is a delightful monograph, with an index deliberately omitted because the book is intended to be read as a whole, describing to the practitioner what measures to follow when he is confronted with a patient who is acutely poisoned.

The author, a resident medical officer for eight years in the Middlesex Hospital, has had much practical experience in the management of such cases. He writes naturally and easily of what the experience has taught him and describes in detail the treatment which he has found successful. The illustrations are a not unimportant factor in making the book more readable.

Any one who picks up the book will read it at one sitting and with enjoyment. It should be made part of the standard equipment of any accident room.

Die seröse Entzündung. By Hans Eppinger, Hans Kaunitz and Hans Popper. Price, 26 marks. Pp. 298, with 124 illustrations and 41 tables. Berlin: Julius Springer, 1935.

In this monograph is assembled a large collection of data from the literature and from the authors' experimental work, dealing with the question of shock. The subject then is elaborated to include general questions of the permeability of membranes. To be fully appreciated the text must be carefully studied, and, while one may not agree with every detail, Eppinger's brilliant thinking is always instructive.